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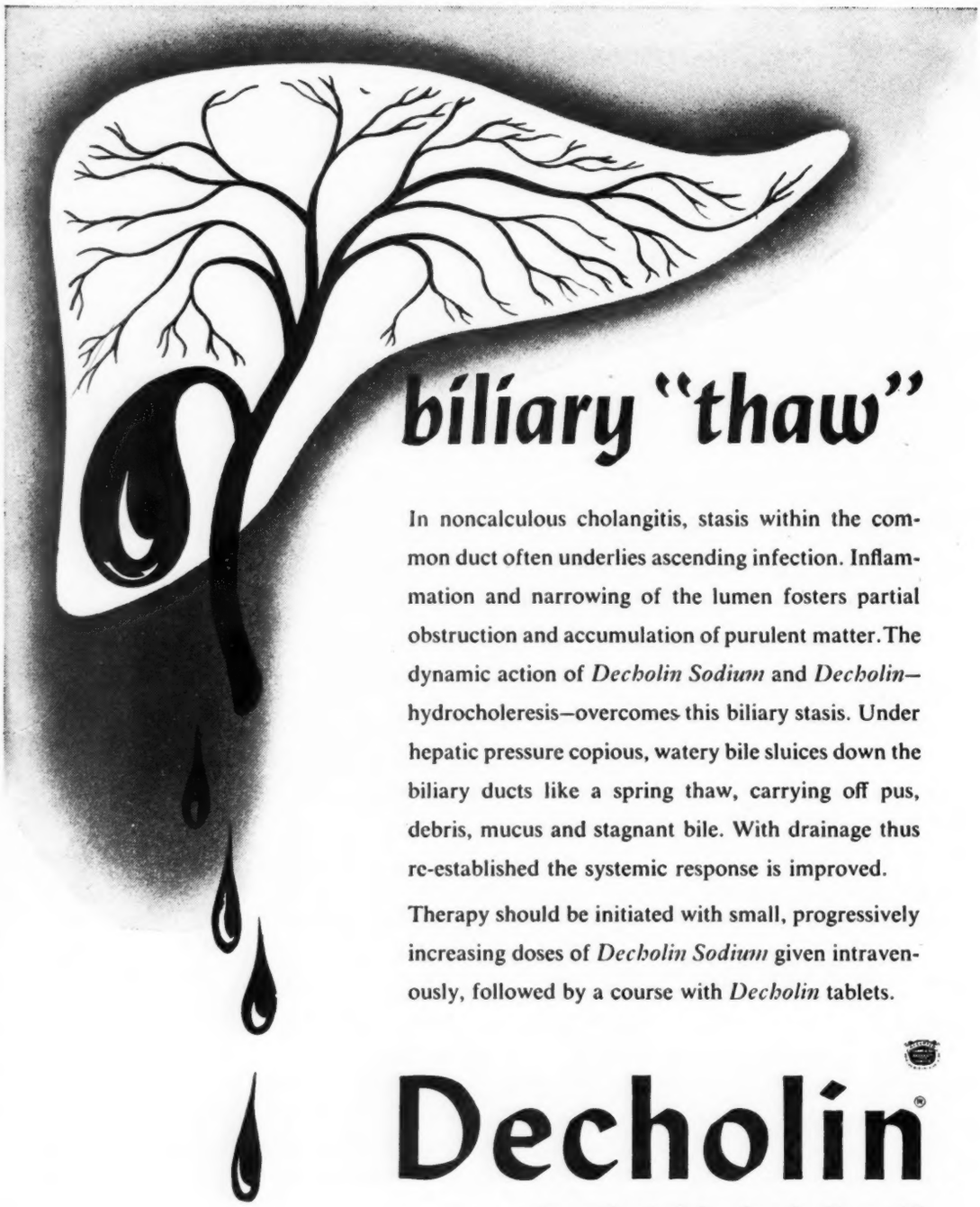

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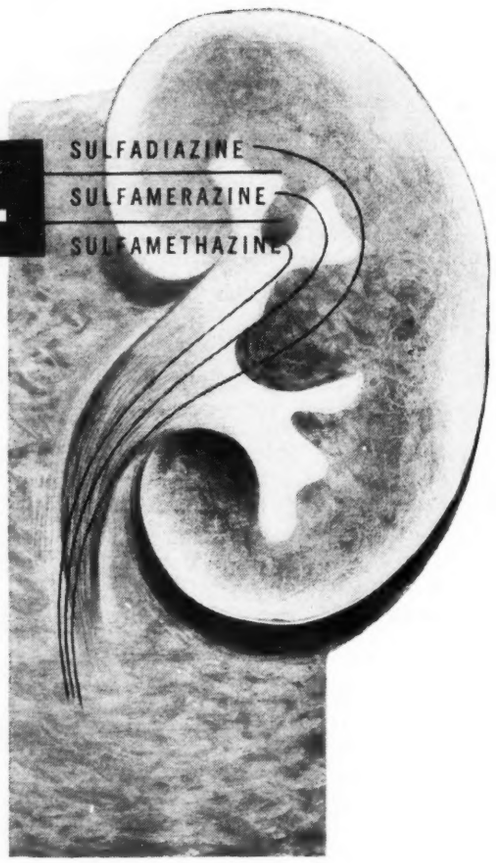

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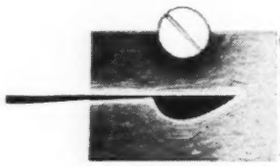

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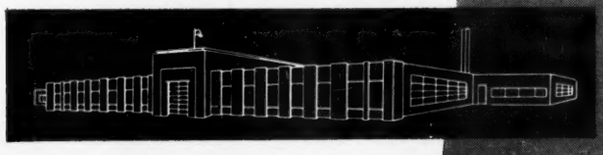

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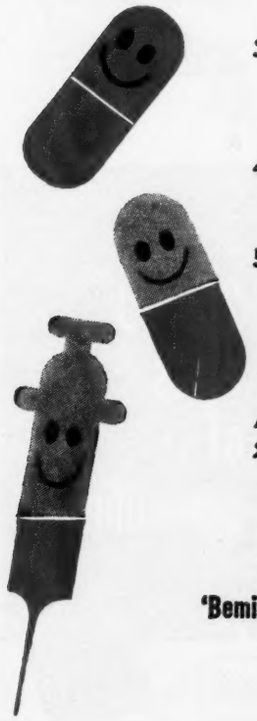

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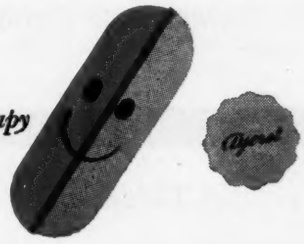

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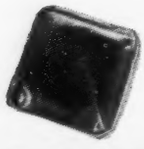

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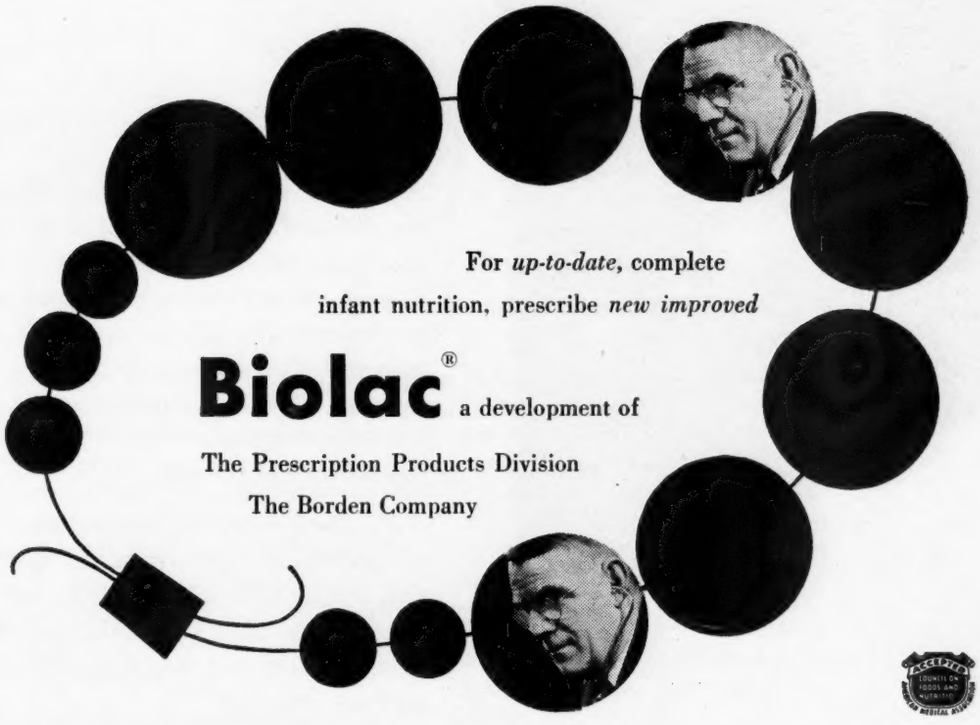

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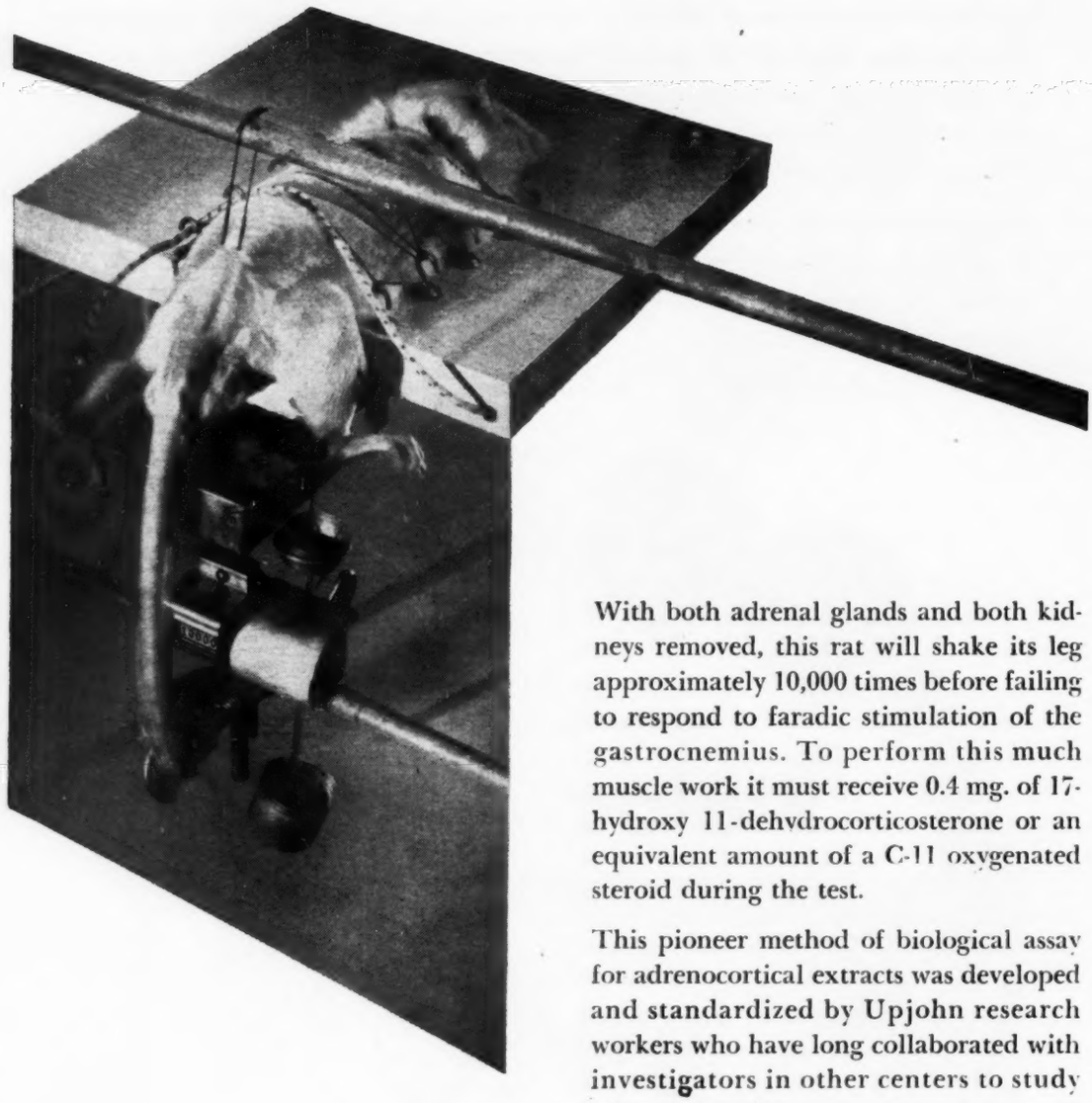

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2. McGavack, T. H. and Klotz, S. D.: Bull. Flower Fifth Ave. Hosp., 9:61, 1946.
3. Weissberg, J., McGavack, T. H. and Boyd, Linn J.: Am. J. Digest. Dis., 15:332, 1948.

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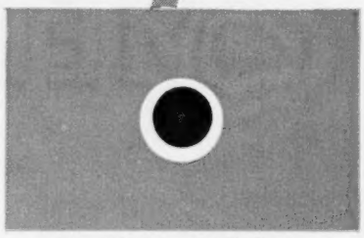

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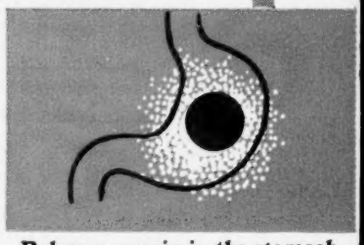

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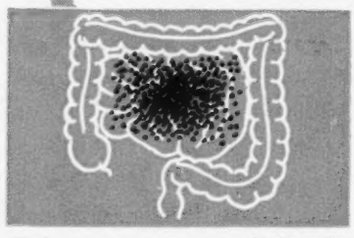

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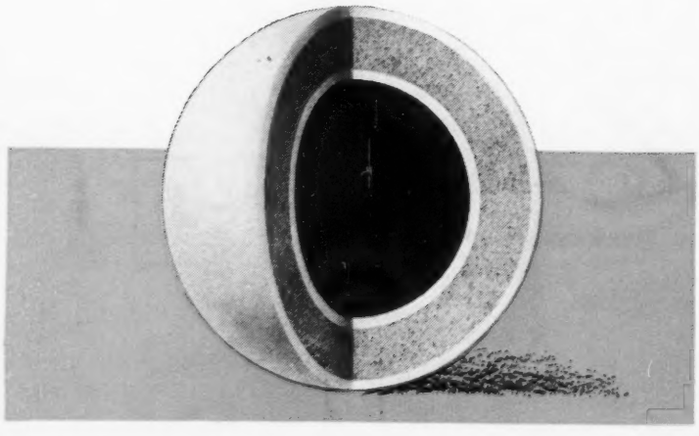

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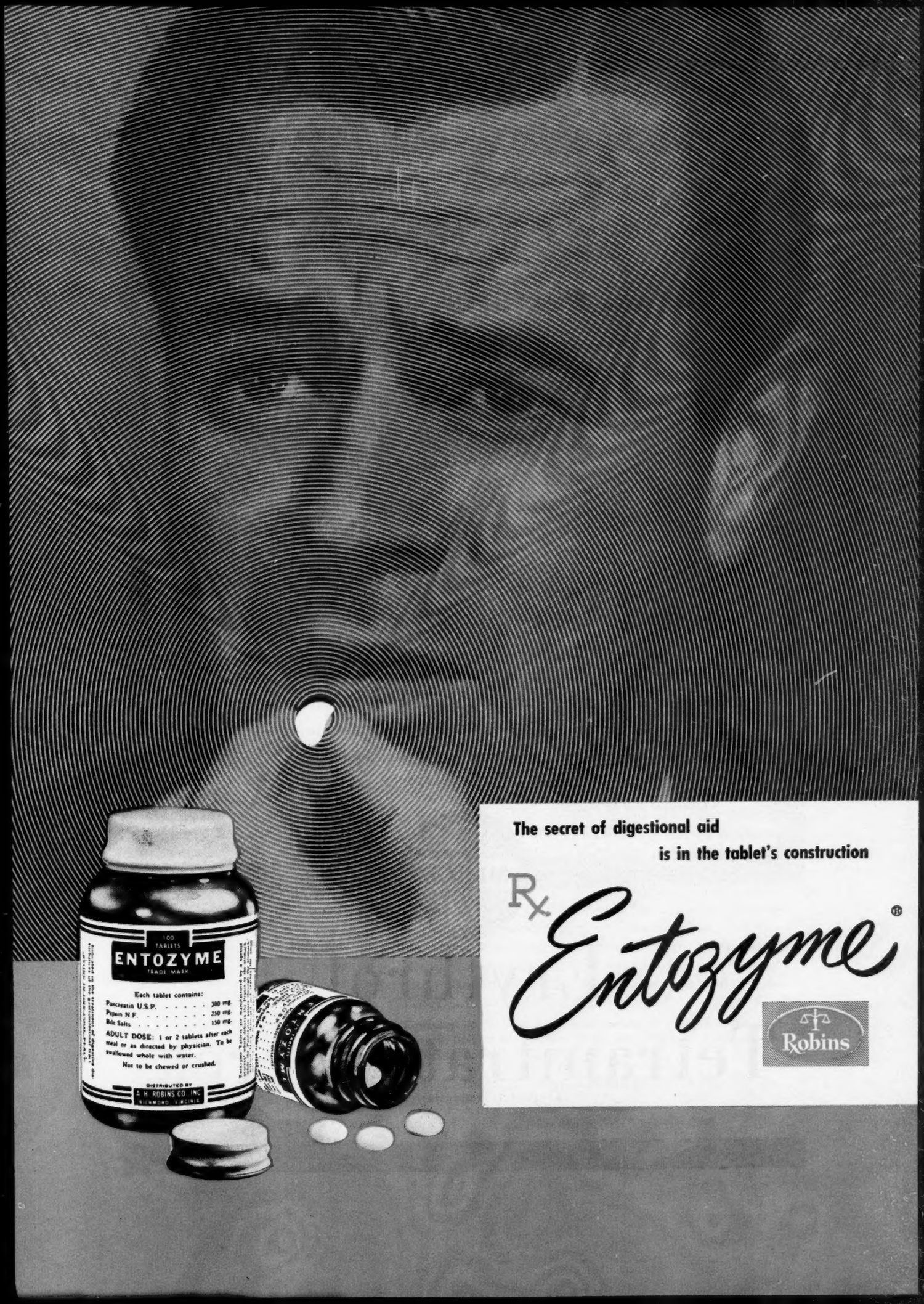
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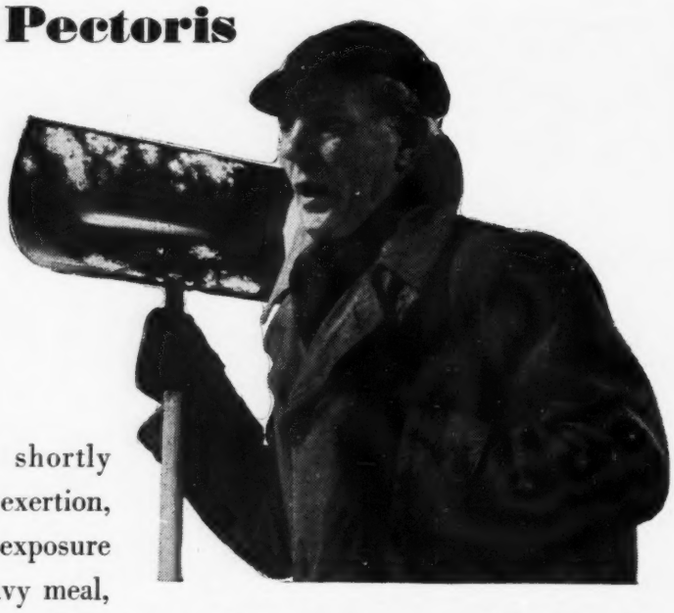

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RAHWAY, N. J.

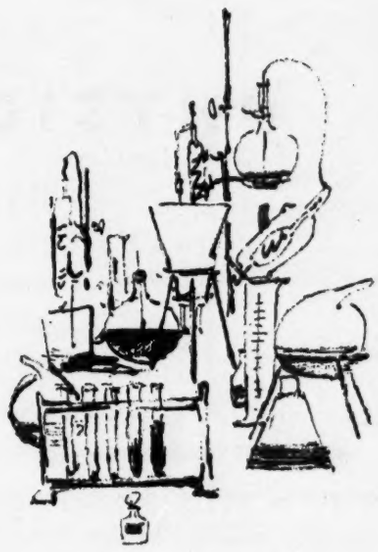
MERCK

Erythrol Tetranitrate Merck

(Erythrityl Tetranitrate U.S.P.)

COUNCIL ACCEPTED

AUREOMYCIN



AUREOMYCIN

HYDROCHLORIDE LEDERLE

in the Pneumonias

Aureomycin possesses a broad spectrum of effectiveness that indicates its use in pneumococcal, streptococcal, staphylococcal and so-called "virus" pneumonias. It has also been shown to be highly effective against *Hemophilus influenzae* and is indicated in infections caused by that organism.

Aureomycin is useful for the control of bacteroides septicemia, brucellosis, Gram-negative infections—including those caused by the coli-aerogenes group, Gram-positive infections—including those caused by streptococci, staphylococci and pneumococci, granuloma inguinale, lymphogranuloma venereum, psittacosis, Q fever, rickettsialpox, Rocky Mountain spotted fever, subacute bacterial endocarditis resistant to penicillin, tularemia, typhus, viral-like and bacterial infections of the eye.

Capsules: Bottles of 25, 50 mg. each capsule. Bottles of 16, 250 mg. each capsule. **Ophthalmic:** Vials of 25 mg. with dropper; solution prepared by adding 5 cc.of distilled water.

LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

30 Rockefeller Plaza, New York 20, N.Y.

for a

PHYSIOLOGIC FALL

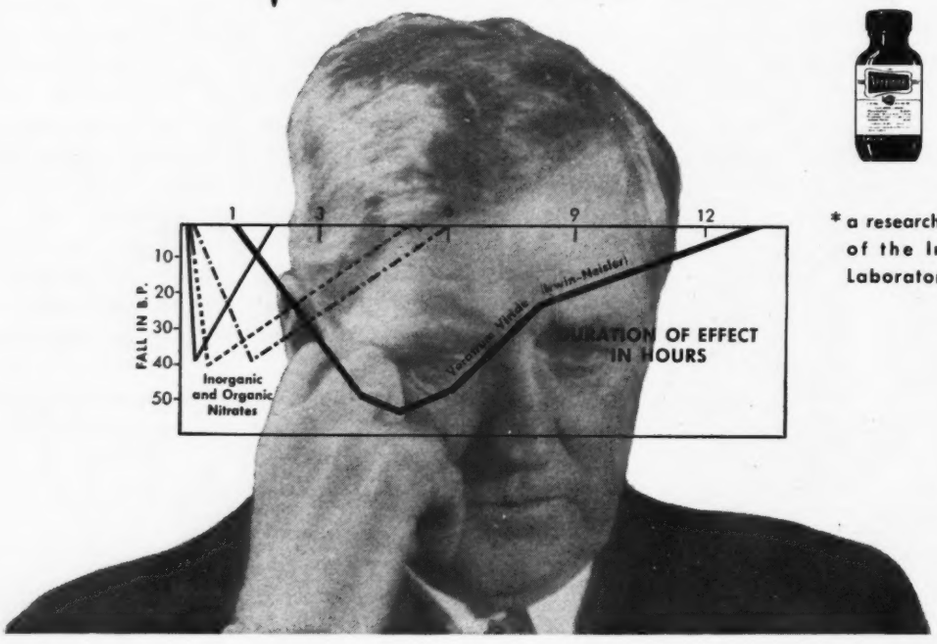
in blood pressure

Of the many drugs used to lower arterial pressure in hypertension, Biologically Standardized veratrum viride (in CRAW UNITS*) is the only drug that produces a physiologic fall in blood pressure. VERATRITE represents a practical modification of this effective hypotensive drug for everyday management of the mild and moderate cases of essential hypertension. Prolonged action, wide range of therapeutic safety and complete simplicity of administration are specific advantages of Veratrite therapy. Each Veratrite Tabule contains: Biologically Standardized veratrum viride 3 CRAW UNITS; sodium nitrite 1 grain; phenobarbital ¼ grain.

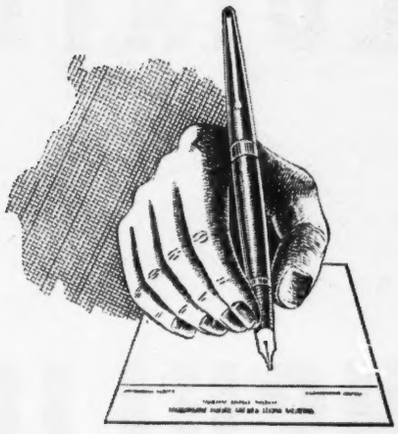
Samples and literature on request.

IRWIN, NEISLER & COMPANY 65 YEAR Irwin DECATUR, ILLINOIS

Veratrite®



* a research development of the Irwin-Neisler Laboratories



in Pyelitis, Cystitis, Prostatitis, and Associated Urinary-Tract Infections

Prescribe

MANDELAMINE®

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

REGISTERED TRADEMARK OF NEPERA CHEMICAL CO., INC., FOR ITS BRAND OF METHENAMINE MANDELATE

the Urinary Antiseptic with

Outstanding Advantages...

1. Wide antibacterial range, including *both* gram-negative and gram-positive organisms
2. No supplementary acidification required (except when urea-splitting organisms occur)
3. Little or no danger of drug-fastness
4. Exceptionally well tolerated
5. No dietary or fluid regulation
6. Simplicity of regimen—3 or 4 tablets t.i.d.

SUPPLIED: Enteric-coated tablets of 0.25 Gm. (3-3/4 grains) each, bottles of 120, 500, and 1,000.

NEPERA

NEPERA CHEMICAL CO., INC.

Pharmaceutical Manufacturers

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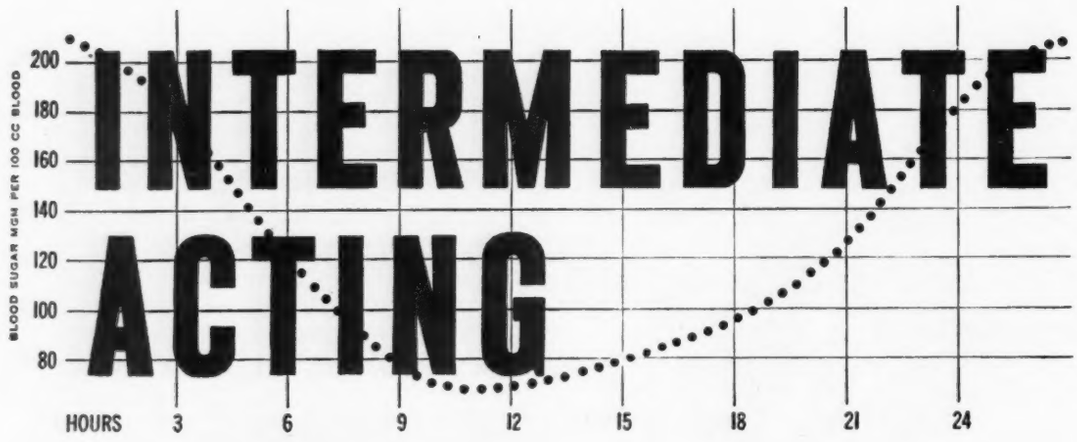


INTERMEDIATE ACTING

GLOBIN INSULIN

'B.W.& CO.'

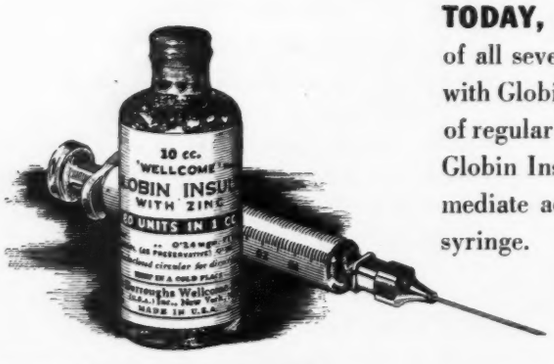
...was developed to fill the "need for an insulin with activity intermediate between that of regular insulin and that of protamine zinc insulin."[1]

IN 1939, Reiner, Searle and Lang described a new "intermediate acting" insulin.

IN 1943, after successful clinical testing, the new substance was released to the profession as 'Wellcome' brand Globin Insulin with Zinc 'B.W. & Co.'

TODAY, according to Rohr and Colwell, "Fully 80% of all severe diabetics can be balanced satisfactorily"[2] with Globin Insulin 'B.W. & Co.'—or with a 2:1 mixture of regular insulin: protamine zinc insulin. *Ready-to-use* Globin Insulin 'B.W. & Co.' provides the desired intermediate action without preliminary mixing in vial or syringe.

In 10 cc. vials, U-40 and U-80.

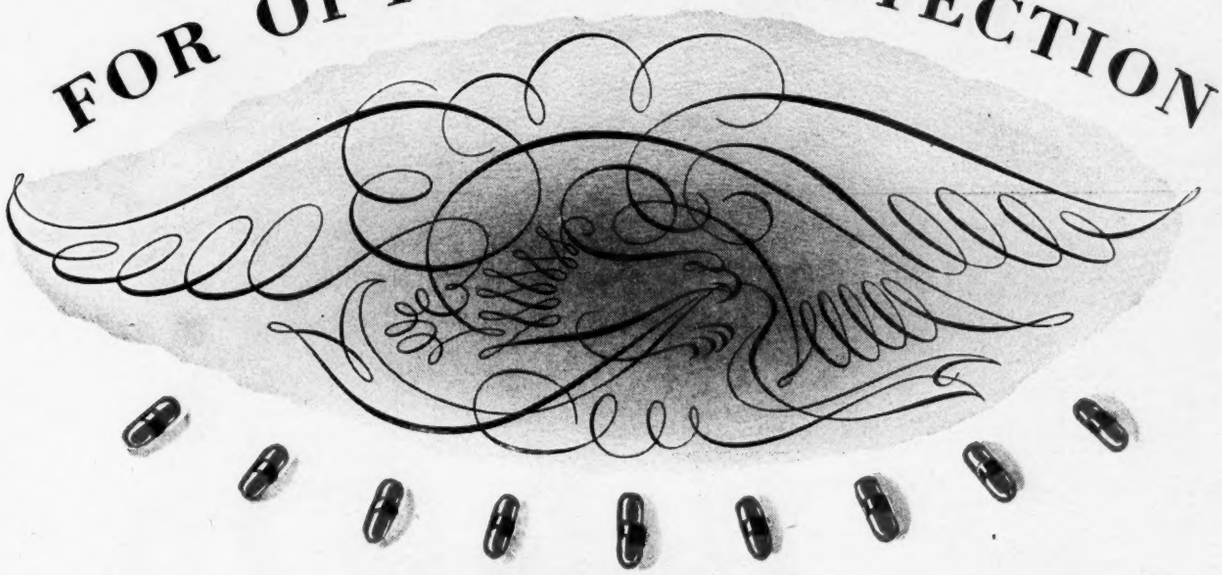


'B.W.& CO. —*a mark to remember*

1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

BURROUGHS WELLCOME & CO. (U.S.A.) INC. Tuckahoe 7, New York

FOR OPTIMUM PROTECTION



nine vitamins

A • B_1 • B_2 • B_6 • Nicotinic Acid • Pantothenic Acid • C • D • E

Nine vitamins—A, the B-group, C, D, E—are available in ABDEC® KAPSEALS® for well-rounded vitamin therapy. You will want to prescribe ABDEC KAPSEALS to overcome vitamin deficiencies quickly and to insure optimal intake of essential nutrients.

ABDEC® KAPSEALS®

comprehensive vitamin therapy

Dosage: For the average patient, one ABDEC KAPSEAL daily; during pregnancy and lactation, two Kapseals daily. Three Kapseals daily are suggested in febrile illnesses, for pre-operative and post-operative patients, and in other situations in which vitamin deficiencies are likely to occur.

EACH ABDEC KAPSEAL CONTAINS

Vitamin A	5,000 U.S.P. units
Vitamin D	1,000 U.S.P. units
Mixed Tocopherols (Vitamin E factors)	5 mg.
Vitamin B_1 (Thiamine Hydrochloride)	5 mg.
Vitamin B_2 (Riboflavin)	3 mg.
Vitamin B_6 (Pyridoxine Hydrochloride)	1.5 mg.
Pantothenic Acid (As the sodium salt)	5 mg.
Nicotinamide	25 mg.
Vitamin C (Ascorbic Acid)	75 mg.

Supplied in bottles of 25, 50, 100 and 250.

PARKE, DAVIS & COMPANY

MEDICAMENTA VERA · P D & CO.

Good nutrition forms the basic background for good health as evidenced in a child's appearance, activity, weight, resistance to infection, and mental outlook. And good nutrition implies especially a well-nourished hemopoietic system—for all the other body tissues depend upon the circulating blood for their nourishment.

Liver, Iron and Red Bone Marrow Armour

(with malt extract), an excellent all-around nutritional adjuvant for children and adults, supplies in particular the essential blood-forming elements necessary to good hemopoiesis. It is also a caloric and physiologic tonic, for patients from infancy to old age.

Available

—regular 8-ounce bottles; also in special two-ounce dropper bottles for infant feeding.

Dosage:

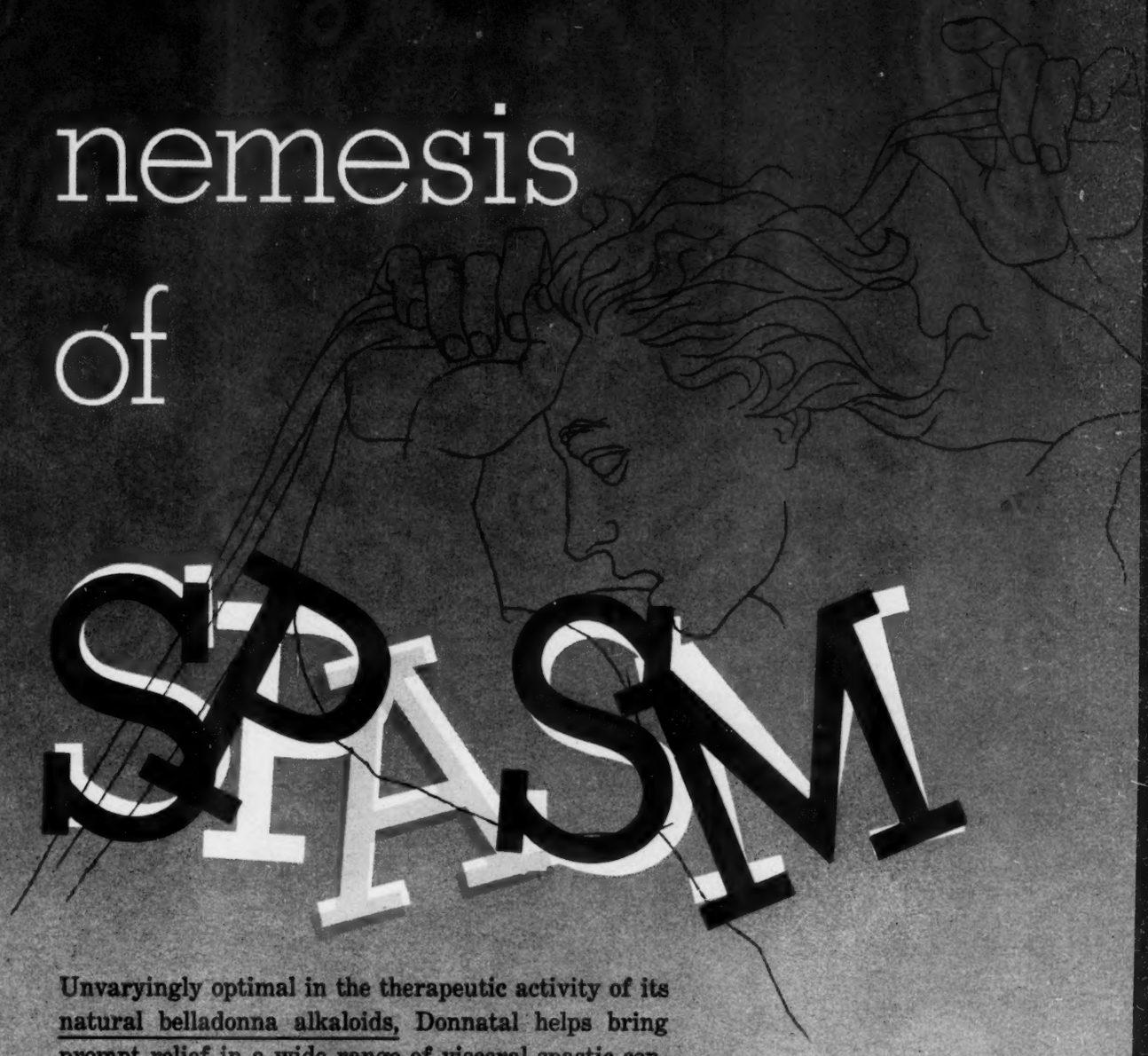
Adults, 2 teaspoonfuls twice daily.
Children under 15—1 teaspoonful twice daily.
Infants—1 to 10 drops daily in milk or water.

Have confidence in the preparation you prescribe — specify "Armour"

ARMOUR *Laboratories*

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS

nemesis of SPASM



Unvaryingly optimal in the therapeutic activity of its natural belladonna alkaloids, Donnatal helps bring prompt relief in a wide range of visceral spastic conditions. Integral with these potent spasmolytic agents is a minimal phenobarbital content, affording practical sedation against psychogenic stimuli. Donnatal's broad professional acceptance stems from its superior efficacy, notable economy, and more-than-marginal safety. Elixir Donnatal constitutes also a highly palatable therapeutic vehicle for adjuvant medication. Available in Tablets, Capsules, and Elixir.

Formula: Each Tablet or Capsule, and each 5 cc. of Elixir contains: Hyoscyamine Sulfate, 0.1037 mg.; Atropine Sulfate, 0.0194 mg.; Hyoscine Hydrobromide, 0.0065 mg.; Phenobarbital (¼ gr.), 16.2 mg.

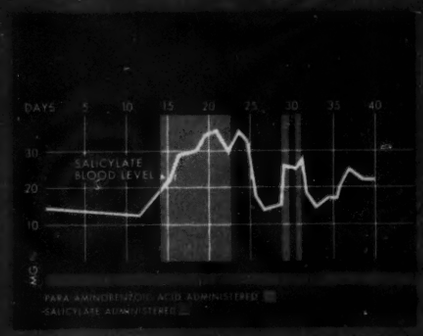
SPASM **donnatal**®

Robins

A. H. Robins Co., Inc. · Richmond 20, Virginia

ETHICAL PHARMACEUTICALS OF MERIT SINCE 1878

Pabalate® produces higher blood salicylate levels



para-aminobenzoic acid increases blood level of concurrently administered salicylate.

The two antirheumatics in Pabalate — sodium salicylate and para-aminobenzoic acid[1] — reciprocally enhance each other's efficacy: para-aminobenzoic acid sharply increases blood levels of the concurrently administered salicylate . . . which, in turn, increases the para-aminobenzoic acid blood level.[2,3] By virtue of this remarkable synergism, many rheumatic reactions may now be given more effective salicylate therapy, particularly in cases resistant to the maintenance of blood levels requisite for clinical response.

Each enteric-coated Pabalate Tablet, or each teaspoonful of the chocolate-flavored Pabalate Liquid, contains sodium salicylate, U.S.P. (5 gr.) 0.3 Gm.; para-aminobenzoic acid, as the sodium salt, (5 gr.) 0.3 Gm.

for better antirheumatic therapy

PABALATE®

the dependable antirheumatic—available in both tablets and liquid, for more convenient administration to patients of all ages!

1. Rosenblum, H. and Fraser, L. E.: Proc. Soc. Exper. Biol. and Med., 65: 178, 1947.
2. Dry, T. L., et al.: Proc. Staff Meetings Mayo Clin., 21: 497, 1946.
3. Belisle, M.: Union Med. Can., 77: 392, 1948.

Robins

A. H. Robins Co., Inc. · Richmond 20, Virginia
ETHICAL PHARMACEUTICALS OF MERIT SINCE 1878

Mrs. Snacker IS A VITAMIN-LACKER

She nibbles and pieces and samples and tastes all day long. In fact, Mrs. Snacker is always hungry—except at mealtime. So her diet too often sidesteps many of the vitamins essential to balanced nutrition. • If there's a better candidate for a subclinical vitamin deficiency than Mrs. Snacker, it might be the hurrier or the worrier, the heavy smoker or the toper. These meal skimpers—vitamin-lackers all—have never learned that unbalanced eating leads to unbalanced nutrition and from there to any number of ills. • In the interval between dietary sin and complete reform, you can't prescribe better vitamin insurance than DAYAMIN. The DAYAMIN capsule is small, has a pleasing vanilla bouquet. Each capsule provides the daily optimum requirements of six essential vitamins, plus pyridoxine and pantothenic acid. One capsule daily as a supplement; two or more for therapeutic use. Your pharmacist can supply them in bottles of 30, 100 and 250.

ABBOTT LABORATORIES,
NORTH CHICAGO, ILLINOIS

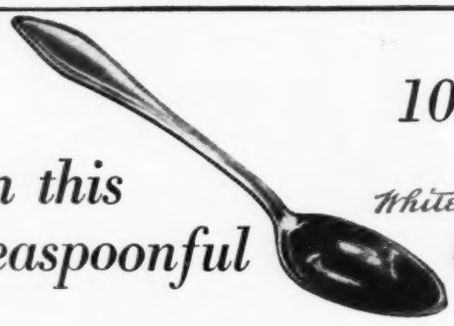
Specify **DAYAMIN®**

(ABBOTT'S MULTIPLE VITAMINS)

Now... ORAL PENICILLIN in 2 new dosage forms..

*50,000 units of penicillin**

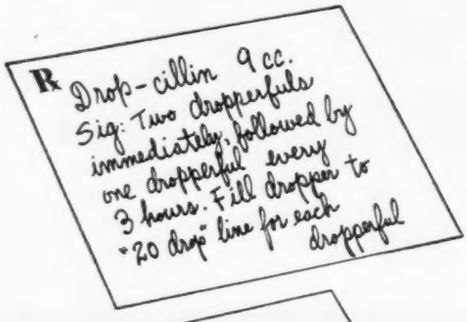
in this dropper White's **drop-cillin**

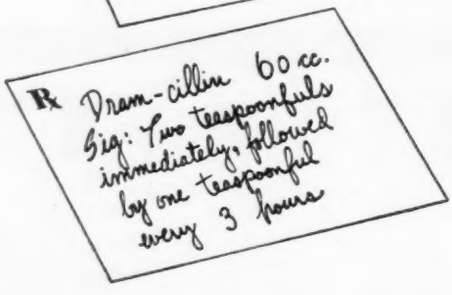


*100,000 units of penicillin**

in this teaspoonful White's **dram-cillin**

... both with a delicious vanilla flavor


℞ Drop-cillin 9 cc.
Sig: Two dropperfuls immediately, followed by one dropperful every 3 hours. Fill dropper to "20 drop" line for each dropperful



SUPPLIED:

DROP-CILLIN—in 9 cc. "drop-dosage" bottles containing 600,000 units of penicillin. Accompanying calibrated dropper (filled to mark) delivers approximately 20 drops (0.75 cc.) containing 50,000 units of penicillin.*

DRAM-CILLIN—in 60 cc. "teaspoonful-dosage" bottles containing 1,200,000 units of penicillin. Each teaspoonful (approx. 5 cc.) provides 100,000 units of penicillin.*

**(*buffered penicillin G potassium*)*

.. more convenient, potent, palatable

White's **DROP-CILLIN** has been specially formulated to provide a "drop-dosage" form of penicillin for oral administration to infants and young children. It may be administered directly or added to the first ounce or two of formula without significantly altering the taste or appearance of the formula.

White's **DRAM-CILLIN** is a most potent liquid oral penicillin. Its pleasant taste and deep ruby-red color appeal to both children and adults alike.

In suitable indicated cases, Drop-cillin and Dram-cillin obviate the use of injections with their attendant fear and discomfort, especially for the young patient. In addition, the nurse or mother is relieved of the chore of crushing tablets and forcing medication upon recalcitrant patients. Full and accurate dosage, with willing adherence to the dosage schedule, is assured.

In prescribing, please note:

***White's* DROP-CILLIN**—50,000 units in one dropperful
***White's* DRAM-CILLIN**—100,000 units in a teaspoonful

Supplied to the pharmacist as a dry stable crystalline powder. Dispensed as freshly prepared solutions, Drop-cillin and Dram-cillin will retain full stated penicillin potency for seven days when refrigerated.

WHITE LABORATORIES, Inc., Pharmaceutical Manufacturers, Newark 7, New Jersey

White's

"A safe and effective drug to use in controlling weight gain during pregnancy."

Coopersmith, B.I.: Dexedrine and Weight Control in Pregnancy, Am. J. Obst. & Gynec. (Oct.) 1949

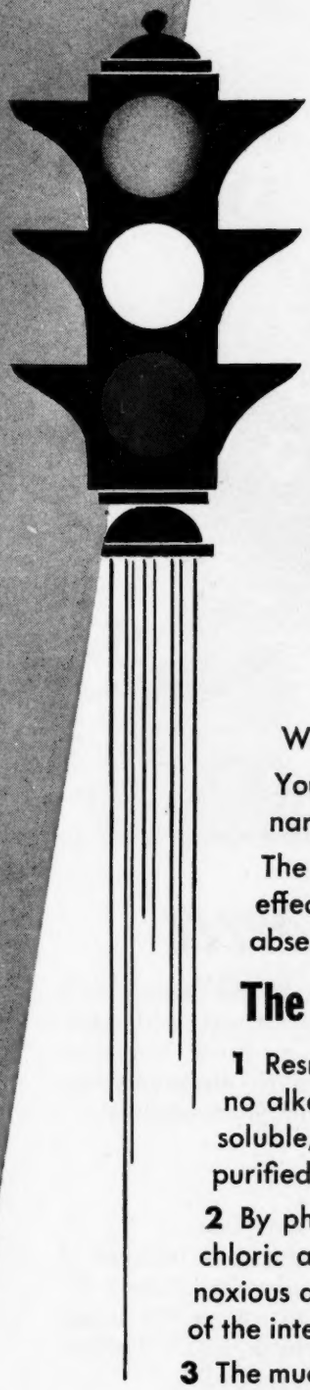
Coopersmith reports the successful use of 'Dexedrine' Sulfate Tablets for weight control in a series of 100 obstetric patients. Because 'Dexedrine' curbed appetite and thus enabled these patients to follow their prescribed diets, control or reduction of weight was achieved in virtually all cases. It is noteworthy that other methods, including the use of thyroid, had previously failed to prevent excessive weight gain in these same individuals. "Thyroid", Coopersmith states, "increases the appetite . . . and is toxic in many cases." "Dexedrine Sulfate", the report concludes, "is a safe and effective drug to use in controlling weight gain during pregnancy."

Smith, Kline & French Laboratories, Philadelphia

Dexedrine* Sulfate tablets • elixir

for control of appetite in weight reduction

*T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.



why you should change to

RESMICON®

mucoprotective acid-adsorbent

We suggest that you treat your peptic ulcer patients with Resmicon.

You may well ask yourself (and us) why you should abandon the ordinary antacids in favor of Resmicon.

The answer is: The gain is great, from the point of view of heightened effectiveness in relief of pain, greater rapidity of healing, and total absence of side effects.

The reasons for this statement? Here they are:

1 Resmicon is not an antacid in the usual sense of the term; it contains no alkalis or amphoteric gels. Resmicon has two ingredients: an insoluble, unabsorbable, non-toxic, ion-exchange polyamine resin; and purified natural gastric mucin.

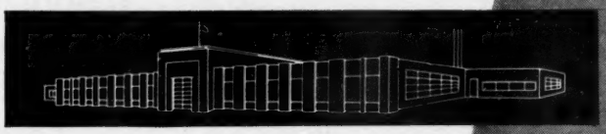
2 By physical adsorption to the resin, the offending factors, hydrochloric acid and pepsin are rapidly removed from their sphere of noxious activity in the stomach and transferred to the alkaline milieu of the intestines where they can do no harm.

3 The mucin protectively coats the damaged gastric mucosa, prevents penetration of acid and pepsin, and facilitates healing.

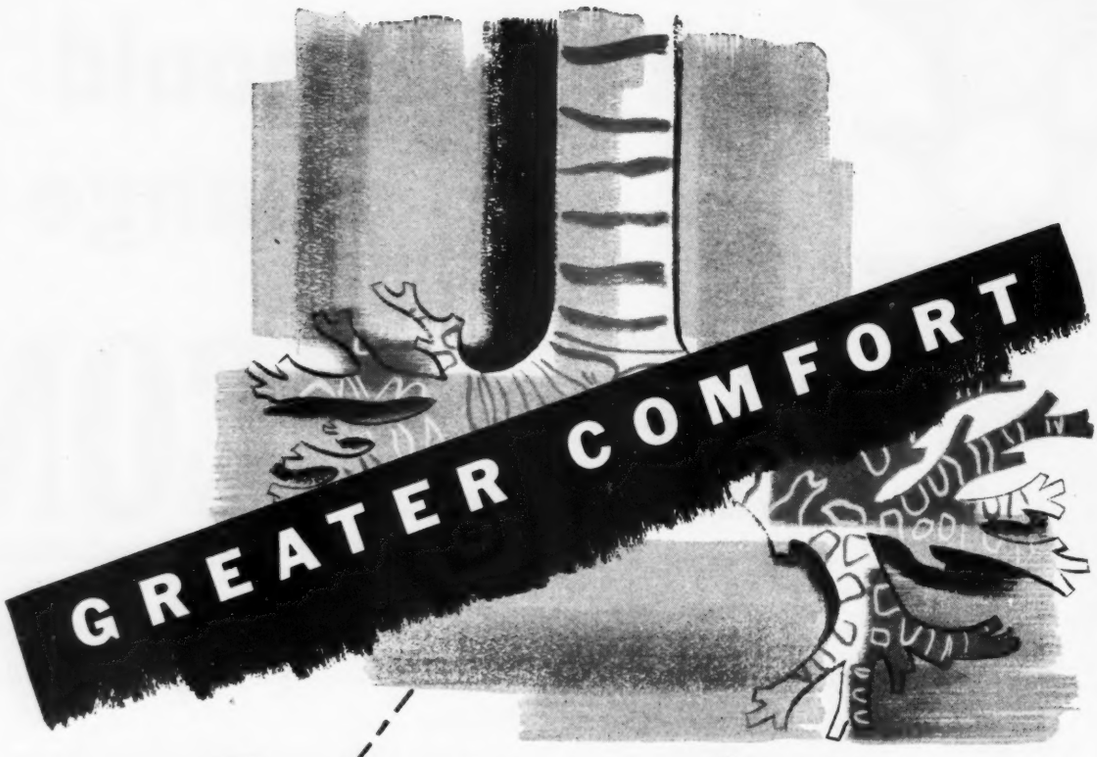
4 Because of its unique mode of action, Resmicon does not cause any distressing side actions so commonly observed with other agents. Thus there are no acid rebound, alkalosis, renal calculi or chloride and phosphate deprivation, as occur with ordinary alkalis (e.g., sodium bicarbonate, calcium carbonate, magnesium oxide, etc.); and no colic or constipation, as may occur with antacid gels (e.g., aluminum hydroxide, silicates, amphoteric gels, etc.).

Resmicon is available in bottles of 84 tablets, each tablet containing 500 mg. anion-exchange polyamine resin and 170 mg. gastric mucin.

If you would like to know more about Resmicon, please write us for our comprehensive booklet.



Whittier
LABORATORIES
Division Nutrition Research Laboratories • Chicago 30, Illinois



in Bronchial Asthma

Elixir Thalfed is a valuable means of producing prompt and prolonged relief from the severe distress of asthma, and minimizing recurrence of paroxysms. It exerts a direct bronchial relaxing influence through the action of its contained aminophylline and ephedrine, and a central action by means of phenobarbital.

Each teaspoonful (5 cc.) provides:

Aminophylline	100 mg. (1½ gr.)
Ephedrine	20 mg. (⅓ gr.)
Phenobarbital	20 mg. (⅓ gr.)

Elixir Thalfed is particularly useful in chronic asthmatic states because of its preventive action against recurrence of seizures and because it combats the frequent tendency to nightly paroxysms. Valuable also in controlling the cough associated with allergic rhinitis and chronic asthmatic bronchitis. Elixir Thalfed is available on prescription through all pharmacies.

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY

SEMCO

Elixir THALFED

to make the
common cold
less common

CORICIDIN*

(antihistaminic—antipyretic—analgesic)

with Chlor-*Trimeton**

antihistaminic therapy

. . . prevents or aborts colds in 90% of cases when initiated within the first hour of symptoms.[1]

. . . shortens duration and decreases severity of an established cold.[1, 2]

. . . reduces the spread of infection to others by eliminating sneezing, lacrimation, rhinorrhea and coughing.[1]

DOSAGE AND TIMING: Two CORICIDIN tablets at the very first indication of a cold, then one tablet every three or four hours for three or four days. In established colds, one tablet every three or four hours for palliative effect.

COMPOSITION: Chlor-*Trimeton* 2.0 mg. (1/30 gr.) with Acetylsalicylic acid 0.23 Gm. (3½ gr.), Acetophenetidin 0.15 Gm. (2½ gr.) and Caffeine 0.03 Gm. (½ gr.).

PACKAGING: CORICIDIN tablets, tubes of 12; bottles of 100 and 1000.

BIBLIOGRAPHY:

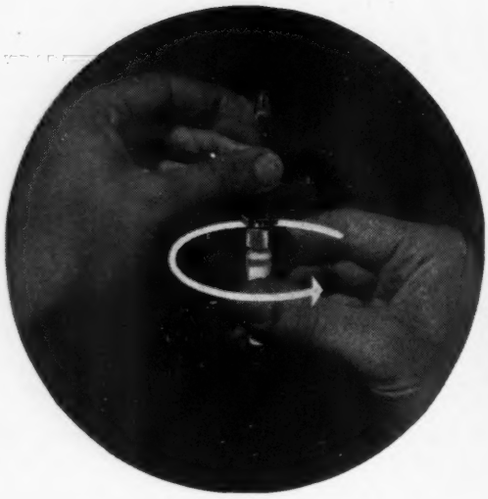
1. Brewster, J. M.: U. S. Nav. M. Bull. *49*:1, 1949.
2. Murray, H. G.: Indust. Med. *18*:215, 1949.

*T.M.

Schering CORPORATION
BLOOMFIELD, N. J.

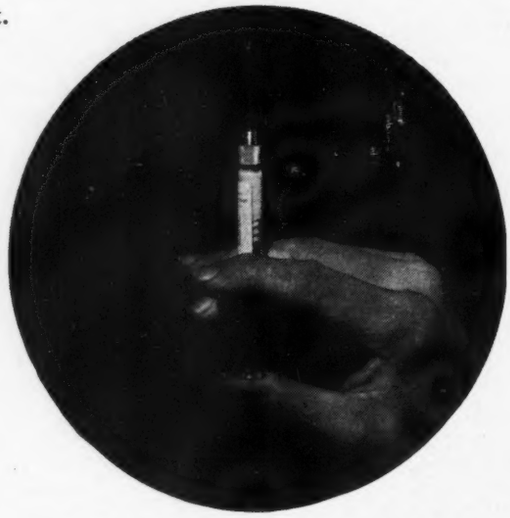
CORICIDIN

SCHERING



two simple twists . . . 5 seconds

Time saving is made easy with the newly designed disposable syringe for **'Duracillin'** (Crystalline Procaine Penicillin—G, Lilly). Just two simple twists of the wrist, and it's ready to use. Because it is presterilized and the dosage premeasured, it eliminates needless bother—saves precious time. Take this less pressing moment to order a supply for the daily occasions when every second counts. Complete literature on disposable syringes for **'Duracillin'** is available from your Lilly medical service representative or will be forwarded upon request.



ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

The American Journal of Medicine

VOL. VIII JANUARY, 1950 NO. 1

Editorial

Potential Hazards of the Newer Insecticides

As a result of the intensive search during the recent war for toxic agents of possible military value thousands of relatively simple chemical compounds were tested and many were found to have a highly specific and potent biologic activity.[1] Since the end of the war many of these compounds have found application for peace-time purposes, some as tools for physiologic and biochemical research, others as potential therapeutic agents, and a very important group as insecticides or rodenticides. As would be expected from the very high order of toxicity of many of these compounds their application to civilian use has been accompanied by the necessity of safeguarding against excessive exposure or overdose. It is of particular importance to point out that some compounds now in use as insecticides and rodenticides are extremely hazardous and physicians must be made aware of their highly potent activity in humans so that fatalities may be avoided.

One of the chemical warfare agents employed as a vesicant during the first World War was Lewisite. Prior to and during the second war, efforts were made to find an effective agent for the treatment of poisoning with this compound. It was found that this and other toxic arsenicals inhibited essential cellular enzymes, including pyruvic oxidases. The enzymes which were particularly sensitive to inhibition were those containing sulfhydryl groups which were essential for their activity, and it was found that arsenicals combined with these sulfhydryl groups. The brilliant work of Peters and his group in synthesizing compounds containing sulfhydryl groups which were found to be capable of protecting and to some extent of restoring the activity of sulfhydryl enzymes by competing with the enzymes for the arsenical compounds is well known. 2,3-dimercaptopropanol (British anti-Lewisite or BAL) was the most practical of these and was soon effectively used in the treatment not only of Lewisite burns but also of systemic arsenical poisoning and of poisoning by the salts of certain other heavy metals.[2]

There are two simple halogen substances, sodium monoiodoacetate and fluoroacetate, both of which are highly toxic to higher organisms. Fluoroacetate is found in nature and has recently been shown to be the toxic principle of a very poisonous South African plant, the toxicity of which has been a problem to cattle men in that region. One mg. of fluoroacetate will usually kill a 200 gm. rat. Convulsions or cardiovascular disturbances predominate in different species of animals. Iodoacetate blocks the activity of enzymes, the effects of which depend on sulfhydryl groups and in this respect iodoacetate resembles the trivalent arsenicals. The most sensitive cellular enzyme is triosephosphate dehydrogenase, so that the supply of energy from carbohydrates is blocked in the early stages of action of these compounds, resulting in interference with cell function. The C-F bond in fluoroacetate is too stable

[1] DALE, SIR HENRY. Science in war and peace. *Nature*, 160: 280, 1947.

[2] Clinical Uses of 2,3-Dimercaptopropanol (BAL). A Symposium. *J. Clin. Investigation*, 25: 451–557, 1946.

to combine by substitution with sulfhydryl groups but this poison both *in vivo* and *in vitro* causes an accumulation of citrate, especially in the kidney, heart and brain. This formation of citrate *in vivo* can be explained upon the hypothesis that the fluoroacetate is activated like acetate in the tricarboxylic acid cycle, and that after formation of the 6-carbon fluoro-acid the cycle is "jammed."[3] According to Hutchens[4] not only acetate oxidation but also pyruvate oxidation and phosphocreatine resynthesis may be inhibited by fluoroacetate. These studies on the mechanism of action of iodoacetate and fluoroacetate provide some insight into the progress of modern biochemistry and show how these highly poisonous substances may be valuable tools of research. On the other hand, fluoroacetate is such a potent rodenticide that it has been marketed commercially and great care must be taken to minimize the hazards due to accidental ingestion by humans.

Intensive work was done during the war on a group of highly toxic fluorine compounds having powerful miotic action, containing the POF group, and known as fluorophosphonates. It was found by investigators in Great Britain that the extremely toxic effects of this group of substances were explicable in terms of their inhibition of the cholinesterase enzymes of the tissues. One of these phosphoric esters, di-isopropyl fluorophosphate (DFP), was found to inhibit cholinesterase enzymes irreversibly. It was discovered that the cholinesterase activity of the various tissues was then restored at rates compatible with the regeneration of new enzyme protein. This facilitated study of the role played by cholinesterase enzymes and the acetylcholine cycle in the function of various body systems. DFP found some clinical application in the treatment of abdominal distention and of glaucoma. A related organic ester of pyrophosphoric acid, tetraethyl pyrophosphate (TEPP), has proved useful in the management of certain patients with myasthenia gravis. Because these compounds inhibit the cholinesterase enzymes of insects and are readily absorbed some of them have proven to be extremely effective as insecticides, particularly TEPP and parathion (p-nitrophenyl diethyl thionophosphate). The latter has recently come to be very widely used as an insecticide in agriculture because it is more effective than DDT against almost all insect parasites, including mites. However, the toxicity of these organic phosphate compounds toward man and domestic animals has resulted in many problems associated with their manufacture and use, whether for therapeutic purposes or as insecticides. Several fatalities in man have already occurred as a result of accidental exposure or indiscriminate use of DFP, TEPP and parathion, particularly the latter substance. Several factors are responsible for the hazards associated with the use of these compounds. First, they are absorbed by any route including the skin, conjunctivae, respiratory and gastrointestinal tracts. Second, because these compounds inhibit cholinesterase enzymes irreversibly or only partly reversibly their effects are long and cumulative. Until the cholinesterase enzymes of the tissues have been restored to normal activity, which may require many days, there is increased susceptibility to the effects of repeated exposure. Third, the cholinesterase enzymes of the tissues can be considerably reduced in activity before symptoms appear. There is a rather narrow margin between the level of cholinesterase activity in the tissues at which symptoms are evident and the level at which death ensues, so that there may be little warning of impending danger following absorption of these substances. Therefore, an understanding of the mechanism of action of these compounds and careful precautionary measures are essential in any situation in which they are handled or used. Physicians should be aware of the present

[3] PETERS, R. A. Biochemical and biophysical aspects of the cell. Summary of address. *Nature*, 164: 392, 1949.

[4] HUTCHENS, WAGNER, PODOLSKY and MCMAHON. The effect of ethanol and various metabolites on fluoracetate poisoning. *J. Pharmacol. & Exper. Therap.*, 95: 62, 1949.

uses of these substances and the hazards involved. Following absorption of toxic amounts of these compounds the most important therapeutic agent is atropine administered promptly and in adequate amounts, which at times may be quite large.[4]

Thus there are many instances in which research concerned with war has led to peace-time applications devoted wholly to human welfare, thereby "turning swords into plowshares." The fields of pharmacology and biochemistry have been advanced by the effort to correlate pharmacologic effects with an understanding of physiologic mechanisms. Many highly toxic substances have found useful purposes. However, there must be a general understanding of the mechanisms of action of these substances and of the hazards involved in their use so that unnecessary accidents can be avoided.

A. McGehee Harvey, M.D.

Clinical Studies

Treatment of Primary Atypical Pneumonia with Aureomycin*

HARVEY S. COLLINS, M.D., E. BUIST WELLS, M.D., THOMAS M. GOCKE, M.D.
and MAXWELL FINLAND, M.D.
Boston, Massachusetts

THE difficulties of reaching definite conclusions concerning the therapeutic effectiveness of any agent in the so-called primary atypical (viral) pneumonias were discussed in a previous communication.[1] Preliminary observations presented in that paper suggested that aureomycin had a beneficial effect on the course of this disease in a small number of consecutive cases. Similar reports on favorable results in small numbers of consecutive cases had been made from two other clinics[2,3] and a third report has since appeared from a military hospital in which one group of patients was treated with aureomycin while alternate patients, serving as controls, were treated with penicillin.[4] The course of the illness under penicillin therapy was quite variable in contrast to the regular and rather prompt improvement that followed the use of aureomycin.

Because of the wide spectrum of antimicrobial action of aureomycin an attempt was made throughout the past year to determine the range of effectiveness of this antibiotic in the various types of pneumonia and other severe respiratory infections which were available to us for study. The present paper deals with observations made in all of the patients who were treated during this year with aureomycin and in whom the diagnosis of primary atypical pneumonia seemed fully justified by the best available clinical and laboratory criteria. The findings in several other aureomycin-treated patients in whom this diagnosis could reasonably be considered will also be presented here and the results in other types of pneumonias will be reported in separate communications.[5,6,7]

MATERIALS AND METHODS

Selection of Cases. For the purpose of this presentation the cases have been divided into three groups.

Group I includes thirty-two patients. They all had the symptoms, physical signs, roentgenographic shadows in the lungs and the common laboratory findings that are generally considered to be characteristic of "viral" or primary atypical pneumonia. Cultures of their blood were negative and no significant pathogens were obtained from their sputum. Cold agglutinins in significant titers were demonstrated at the proper stage of the disease in the serum of every one of these patients and in most instances marked rises in titer were observed. These thirty-two patients may be considered as representing the most clearly defined cases of primary atypical pneumonia.

Group II includes eight patients. The findings in these cases were comparable in every respect to those in Group I except that cold agglutinins could not be demonstrated in any of their sera.

Because of the paucity of characteristic cases of primary atypical pneumonia suitable for this study only one-fourth of the cases in Groups I and II were from the Medical Services of the Boston City Hospital. One-half of all the cases in these two groups were observed in ten other hospitals in and around Boston. The remaining eight patients were treated at home, the majority

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass. Aided by a grant from the United States Public Health Service.

by two colleagues who made most of the essential clinical and laboratory observations and provided the materials for other relevant laboratory tests.

There was an equal number of males and females in each of these two groups. In age these patients ranged from ten to sixty-one years but most of them were young adults; only five were under twenty, five others were over forty years old. (Table I.)

TABLE I
AGE AND SEX DISTRIBUTION OF FORTY PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA TREATED WITH AUREOMYCIN—1948–1949

	No. of Patients*	
	Group I	Group II
Sex:		
Males	16	4
Females	16	4
Age (years):		
19 or less	5	0
20–29	17	3
30–39	8	2
40–61	2	3

* Group I: 32 characteristic cases in which cold agglutinins were demonstrated in significant or rising titer.

Group II: 8 similar cases in which cold agglutinins were not demonstrated.

Group III includes nine patients with acute pulmonary infections in whose sera cold agglutinins were demonstrated in significant titers or in low but rising titers but the diagnosis of primary atypical pneumonia was discarded in each instance, with one possible exception. These nine patients, who form a heterogeneous group, were from the medical wards of the Boston City Hospital and they will have to be considered individually.

Serologic Tests. Serial samples of blood for serologic tests were obtained at suitable intervals from most of the patients but in five cases single specimens only were obtained after the middle of the second week of the disease. The blood was warmed to 37°C. before separating the clot and the serum was removed carefully to avoid including any cells. When not in use the sera were stored in rubber-stoppered pyrex tubes, most of them at −25°C. and the rest in a household refrigerator at 5°C.

Tests for cold agglutinins were done by a method previously described[8] except that the group O blood for the cell suspensions was taken in Alsever's Solution Number II[9] and these cells were used in a final concentration of 0.5 per cent. The tests for Streptococcus MG agglutinins were made as in previous studies[10] except that the antigen was prepared from strain MG 9, furnished by Dr. Harry S. Ginsberg of the Hospital of the Rockefeller Institute for Medical Research and the organisms were heated at 65°C. for thirty minutes before they were washed and resuspended.* The tests for influenza viral antibodies were carried out as in other studies,[11] using the inhibition of chicken cell agglutination with the PR8 strain of influenza A and the Lee strain of influenza B. The titers given in the tables and charts are expressed as the reciprocal of the final dilution of serum. These tests were all performed by Mrs. Mildred W. Barnes.

TABLE II
ANTIMICROBIAL THERAPY USED BEFORE AUREOMYCIN WAS STARTED

Therapy	No. of Patients*	
	Group I	Group II
Penicillin	13	2
Sulfadiazine	1	3
Penicillin and sulfadiazine	11	
Penicillin and streptomycin	1	
None	6	3

* See footnote to Table I.

Complement fixation tests for psittacosis and Q fever were also carried out with the acute and convalescent phase sera from most of these patients. Some of these tests were done in the Department of Virus and Rickettsial Diseases of the Army Medical Center through the courtesy of Dr. Joseph E. Smadel and Dr. Ross L. Gauld, and others in the Section of Viral and Rickettsial Research of the Lederle Laboratories through the kindness of Dr. Herald R. Cox. The antigen for the tests for psittacosis done in the former laboratory was the "P4 strain of ornithosis," while the 6BC strain of psittacosis was used in the latter. The antigen used in the tests for Q

* Suggested by Dr. Edward C. Curnen in a personal communication.

fever in both laboratories was prepared from the American "Nine Mile Strain."

STATUS OF THE PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA AT THE TIME AUREOMYCIN WAS STARTED

Previous Therapy. Other antimicrobial therapy (Table II) had been given to most of the patients before aureomycin was started. Such therapy had been administered over a period ranging from one to seven days but in seventeen of the patients it had been used for only two days or less. In no instance, however, was there evidence of any sustained benefit from these agents and in most of the patients the symptoms increased and the pulmonary lesions extended while they were being given. In nine patients these agents had been discontinued one or more days before aureomycin was started and in most of the others they were stopped at that time. An analysis of the condition of the forty patients at the time aureomycin was begun is shown in Table III.

TABLE III
STATUS OF THE DISEASE AT TIME AUREOMYCIN WAS STARTED IN FORTY CASES OF PRIMARY ATYPICAL PNEUMONIA 1948–1949

	No. of Patients	
	Group I	Group II
Day of disease:		
1–3	2	4
4–5	8	1
6–7	5	1
8–10	13	1
11–14	2	1
15 or later	2	
Temperature F:		
100°–101.9°	8	1
102°–103.9°	14	4
104° or higher	10	3
Leukocytes per cu. mm.:		
7,400 or less	12	3
7,500–9,900	4	3
10,000–12,400	8	1
12,500 or more	3	
Not done	5	1
Extent of lung involved:		
Unilateral:		
1 lobe or less	14	3
More than 1 lobe	1	
Bilateral:		
2 lobes or less	6	5
3 lobes	4	
More than 3 lobes	7	
Severity of illness:		
Mild	9	2
Moderate	14	5
Severe	6	1
Critical	3	

Duration of Disease. In fifteen of the thirty-two patients in Group I and in six of the eight in Group II the first dose of aureomycin was given during the first week of the disease. Two patients were treated after the end of the second week; in Case 5 (M. C., shown in Figure 2 in the earlier paper[1]) aureomycin was first given on what was considered to be the nineteenth day and in Case 31 it was started on the fifteenth day. The former was critically ill at the time while in the latter the symptoms were only of moderate severity but there was extensive pulmonary involvement and considerable respiratory distress at the time.

Height of Fever. All of the patients were febrile when aureomycin was started. In three-fourths of the patients the temperature at that time was 102°F. or higher and in one-third of the patients it was 104°F. or higher.

Leukocyte Counts. The total leukocyte counts were normal or slightly elevated in most instances. In three patients, all of them critically ill at the time, the white blood counts were between 16,000 and 20,000 when aureomycin was started. There were three additional patients in whom white blood counts of 15,000 or higher had been obtained on some occasions prior to treatment but their counts dropped to more nearly normal levels by the time aureomycin treatment was begun.

Lung Involvement. The extent of the pulmonary lesion was estimated as nearly as possible from the physical examination and roentgenograms. Bilateral involvement was more frequent than unilateral lesions, but extensive infiltrations of the miliary type, involving most of both lungs, were present in only seven of the patients.

Severity. An attempt was made roughly

to assess the severity of the disease from the intensity of the symptoms, the appearance of "toxicity," degree of cyanosis and respiratory distress and other evidence of acute illness. About one-half of all of the patients were considered to be moderately ill; in about one-fourth of the patients the disease was considered to be mild and the others were severely or critically ill when aureomycin was started.

DOSAGE OF AUREOMYCIN

Almost all of the aureomycin* used in the present cases was given by mouth. The last patient to be treated, Case 32, received the antibiotic intravenously only and one other patient (E. S., Case 11) received part of the treatment intramuscularly. No attempt was made to determine the optimum dosage or duration of therapy and a number of the patients, particularly some of the first to be treated, were deliberately given larger doses and these were maintained for longer periods than was deemed necessary according to their response. An analysis of the dosage used in all of the forty patients is given in Table IV.

In most of the patients treatment was started with doses of 1 gm. every four or six hours and this schedule was usually maintained but in some patients the individual dose was decreased or the interval between doses was increased after the temperature reached normal and the acute symptoms subsided. In one-fourth of the patients individual doses of 0.5 gm. were given every two, four or six hours from the start and the shorter intervals were lengthened after the patient improved.

The total dose varied in different patients between 3 and 44 gm. and was given over a period ranging from one to thirteen days. Most of the patients received less than 15 gm. within a period of less than four days. The average total dose for all of the forty patients was 12.3 gm. given over an average of 3.6 days. If four of the earliest cases receiving the largest doses are omitted, the remaining patients of both groups received an average of 10.1 gm. in three days.

EFFECT OF AUREOMYCIN ON THE COURSE OF THE DISEASE

The general nature of the effect of aureomycin on the clinical course in the first few cases of this series has already been described in the preliminary report,[1] in which the histories of four of these patients were presented. The relevant clinical and laboratory findings and the course of the disease in five additional cases which illustrate a variety of responses to therapy are shown in Figures 1 and 2. It was entirely impractical in this study to observe any sort of alternate or parallel series of comparable control cases not treated with aureomycin.

TABLE IV
ANALYSIS OF DOSAGE OF AUREOMYCIN USED IN FORTY PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA
1948–1949

	No. of Patients	
	Group I*	Group II
Dosage schedule (by mouth)		
1.0 gm. every 4 hours	14	3
1.0 gm. every 6 hours	10†	2
0.5 gm. every 2 hours	5	1
0.5 gm. every 4 hours	2	1
0.5 gm. every 6 hours	..	1
Total dose by mouth		
9 gm. or less	9	5
10–14 gm	15†	2
15–19 gm	3	1
20 gm. or more	4	
Average	(13.3 gm.)‡	(10.1 gm.)
Total duration of treatment		
48 hours or less	7	0
48–72 hours	9	6
72–96 hours	10	
96–120 hours	3	2
7–13 days	3	
Average	(3.7 days)‡	(3.2 days)

* 1 patient received the antibiotic only intravenously; 500 mg. followed by two doses of 250 mg. at twelve-hour intervals.

† One of these patients also received three intramuscular doses of 80 mg. each.

‡ Four of the first six patients studied received doses of 25–44 gm. (average 35 gm.) in from 4–13 days (average 9 days). If these 4 are excluded, the remaining patients in Group I received an average of 10.1 gm. in 3 days.

* The aureomycin was supplied by Lederle Laboratories.

The results can therefore be presented only with respect to the temporal relation between the administration of aureomycin and the clinical course of the disease as observed in all of the patients. An analysis of the effect of the therapy on the fever and afebrile by the end of the second day. Only four patients still had low-grade fever more than three days after aureomycin was started. In two patients in whom treatment was discontinued after one day and in patient E. S. who was given intramuscular doses

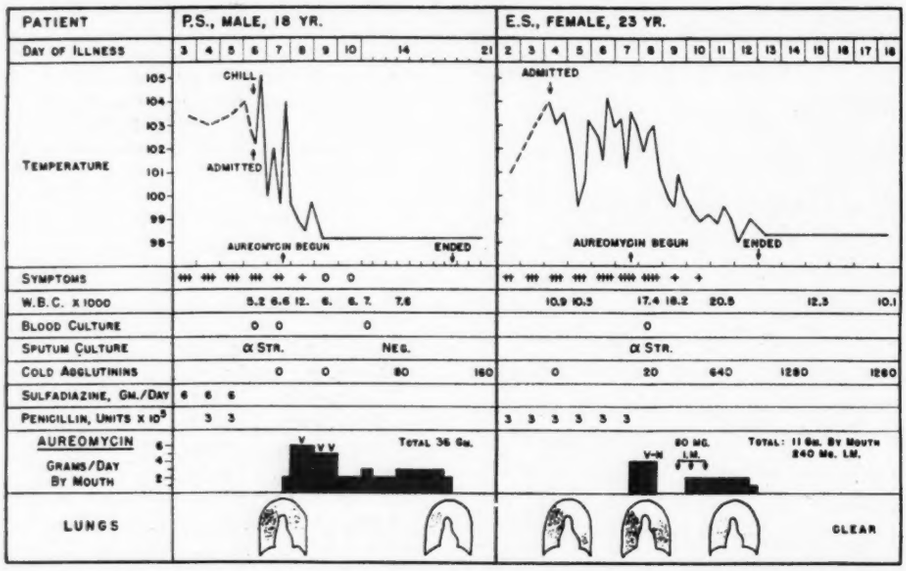


FIG. 1. Relevant findings in two patients with primary atypical pneumonia treated with aureomycin.

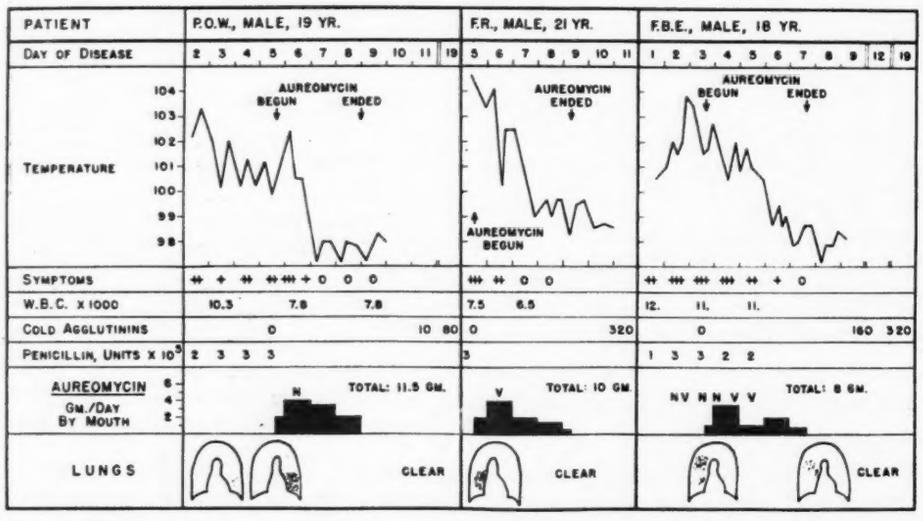


FIG. 2. Findings in three additional patients with primary atypical pneumonia treated with aureomycin.

on the acute symptoms as well as a general estimate of the effect of the antibiotic on the course of the disease is given in Table v.

Effect on the Fever. The great majority of the patients had a significant drop in temperature within twenty-four hours after the first dose of aureomycin and were essentially after the first day of oral therapy, the favorable course was interrupted or a relapse of fever and symptoms occurred, but resumption of oral dosage was followed by a subsidence of the fever.

The relation of the fever to the administration of aureomycin in each of the forty

patients is shown graphically in Figures 3 and 4. From these serial charts which are arranged in order of the duration of illness at the time when aureomycin was started, it appears that the fever responded quite regularly in all cases although the drop in temperature was not equally precipitate in every instance. These charts also indicate that, in general, the response of the fever was independent of the duration of the disease when aureomycin was started.

Effect on Symptoms. Symptomatic improvement as indicated by relief of headache, cerebral dysfunction, malaise, chilly sensations, sweats, soreness of the chest, dyspnea, cyanosis, etc., generally paralleled the drop in temperature. In some of the patients in whom fever continued for more than a day after aureomycin was started subjective improvement preceded the subsidence of fever. While the cough also improved with the other symptoms and became less irritating in most cases, some of the patients continued to cough for several days after they appeared to be otherwise completely well. Hoarseness also continued for several days in two patients.

Effect on the Pulmonary Lesion. There was no definite evidence of extension of the lesion in the lungs after the initiation of aureomycin therapy. In at least two patients, however, rales first became evident on the day after treatment was started over new areas of the chest where they had not previously been heard, but pulmonary infiltrations were seen in that region in early roentgenograms in one of these patients. In two other patients the signs apparently extended or reappeared when treatment was stopped because of vomiting after only three or four doses had been taken.

The rapidity with which the lesions resolved was difficult to assess with any degree of accuracy because roentgenograms were not taken at frequent enough intervals in most patients while others were discharged from the hospital before their lungs had cleared. In twenty-three of the patients of Group I and in six of Group II the clinical and roentgenographic data were sufficient to give some indication of the time when the lungs cleared. Among the former definite clearing was noted within two days after aureomycin was started in six patients, on the third or fourth day in ten and between the fifth and seventh day in seven;

TABLE V

RESULTS OF AUREOMYCIN THERAPY IN FORTY PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA—1948–1949

Effect of Therapy	No. of Patients	
	Group I	Group II
Interval from first dose to first major and sustained drop in temperature:		
less than 12 hours	7	3
12–24 hours	20	1
25–36 hours	3	2
37–48 hours	1	1
49–72 hours	1	1
Total duration of fever (>99°F.) after first dose:		
less than 12 hours	3	1
12–24 hours	14	2
25–36 hours	6	2
37–48 hours	4	1
49–60 hours	2	1
4–7 days	3	1
Interval from first dose to major symptomatic improvement:		
less than 24 hours	26	6
25–48 hours	6	1
49–72 hours	..	1
Total duration of significant symptoms (except cough) after first dose:		
24 hours or less	9	3
25–48 hours	19	3
49–72 hours	2	1
73–96 hours	1	1
5 days	1	
Estimation of effect of aureomycin		
1. Marked improvement directly related to onset of treatment		
(a) definitely or reasonably ascribable to aureomycin	19	3
(b) may have been coincidental	2	3
2. Definite improvement in relation to onset of treatment		
(a) reasonably ascribable to aureomycin	2	
(b) may have been coincidental	5	2
3. Considerable improvement directly related to aureomycin but result obscured, in part, by inadequate treatment due to nausea and vomiting	4	

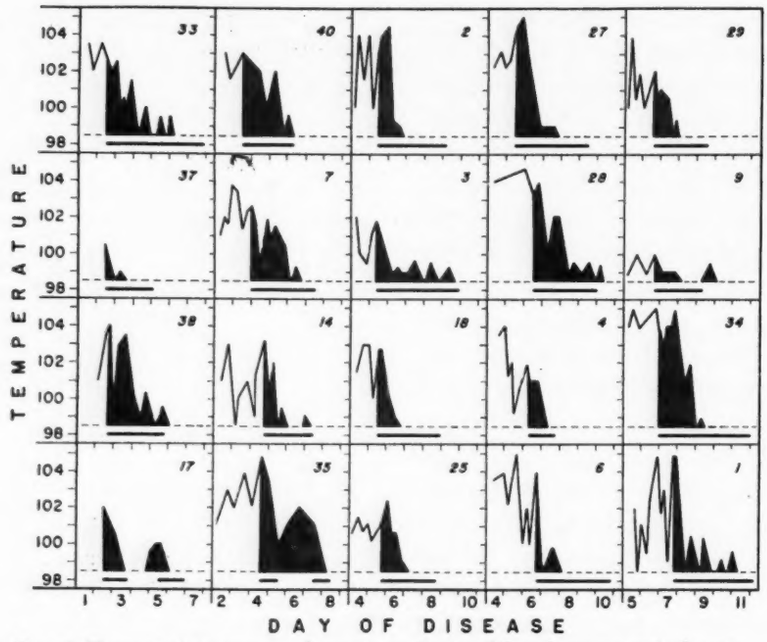


FIG. 3. Temperature curves of twenty patients with primary atypical pneumonia in whom aureomycin was begun during the first week of the disease. The cases are arranged according to the duration of symptoms at the time treatment was started. The solid bars under each curve indicate the period during which the aureomycin was given.

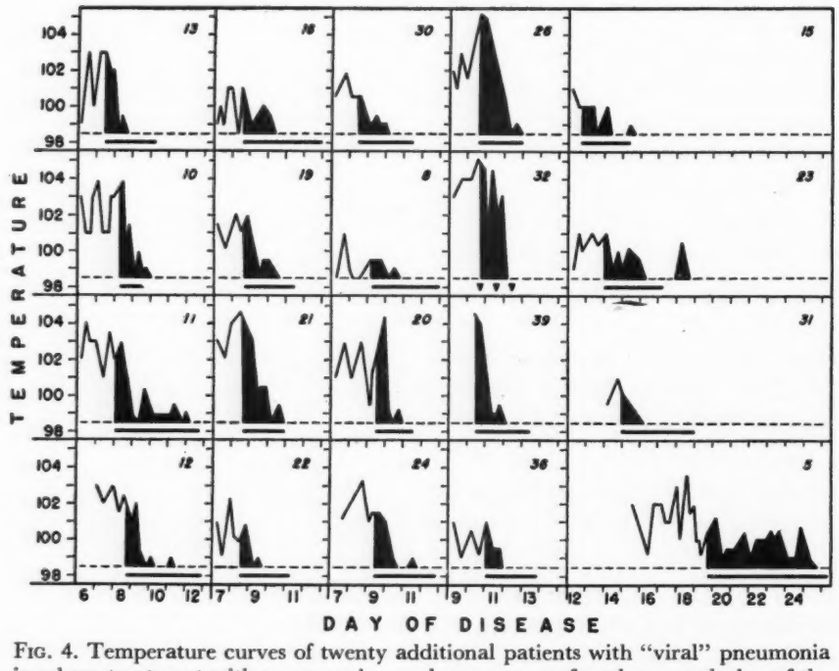


FIG. 4. Temperature curves of twenty additional patients with "viral" pneumonia in whom treatment with aureomycin was begun on or after the seventh day of the disease. The solid triangles in Case 32 represent individual intravenous doses.

complete clearing was demonstrated by physical signs and by x-ray in less than ten days in nineteen patients, whereas in four others infiltrations were still demonstrable more than ten days after aureomycin was begun. In Group II evidence of some clearing was obtained within the first two days in two cases, on the third or fourth day in three and on the sixth day in one patient. In the first five of these six patients the lungs were completely clear to physical and x-ray examination within ten days after the first dose of aureomycin.

Estimation of the Beneficial Effect of Aureomycin. An attempt was made to evaluate the effect of aureomycin in each of the patients on the basis of all of the available observations and the results are also shown in Table V. Definite to marked improvement occurred in every patient within the first day or two after aureomycin was started but in some instances the condition of the patient at that time was such that the improvement may have been coincidental or at least could not with any assurance be ascribed to the action of the antibiotic. In about two-thirds of the patients, however, prompt and definite improvement could quite reasonably, if not with certainty, be ascribed to the favorable effects of the antibiotic and in many of these patients the effects could be described as dramatic.

There were no complications in any of the patients in Groups I and II.

RESULTS OF SEROLOGIC TESTS

Cold Agglutinins. Among the patients in Group I there were fifteen in whom the initial serum obtained at or just before the time aureomycin was started showed no cold agglutinins or, in one instance, only slight agglutination (+) in the lowest dilution used, namely 1:10. These sera were obtained on or before the sixth day of the disease in nine of these fifteen patients and on the seventh or eighth day in the other six. In all of these fifteen patients subsequent serum specimens yielded cold agglutinin titers ranging from 1:80 to 1:2560, most of them being 1:320 or higher.

There were eight patients in whom the initial sera obtained at about the time aureomycin was first given yielded cold agglutinin titers ranging from 1:20 to 1:80. One of these sera was obtained on the fifth day (titer 1:80) and the other seven were obtained on the seventh to the ninth day. In one additional patient a titer of 1:640 was obtained when treatment was started on what was estimated to be the nineteenth day. Later specimens of serum from each of these nine patients showed an increase in titer ranging from 4-fold to 32-fold.

In the remaining eight patients of Group I the initial or only specimen of serum tested showed cold agglutinin titers ranging from 1:40 to 1:2560 but these sera were obtained between the tenth and twenty-fourth day of the disease. In six of these eight patients treatment with aureomycin had been started from one to nineteen days before this specimen was obtained.

It is thus seen that significant titers of cold agglutinins were demonstrated at the appropriate time in the course of the disease in every one of the thirty-two patients in Group I. Furthermore, either the first appearance of cold agglutinins or a significant rise in titer was demonstrated in the serum of every one of these patients in whom an initial specimen was obtained before the middle of the second week of the disease.

Streptococcus "MG" Agglutinins. Agglutinins for Streptococcus MG were also demonstrated in the serum of most of the patients of Group I. The titers were not usually so high and rises in titer were not so striking nor were they demonstrated as often as was the case with cold agglutinins. Furthermore, in four of the thirty-two patients the development of agglutinins for Streptococcus MG could not be demonstrated in serial samples of serum obtained at appropriate times, while in six others the sera yielded titers of only 1:20 or less and serial specimens showed only a 2-fold change in titer or none at all.

In the eight patients of Group II in whom cold agglutinins were not found the tests for Streptococcus MG agglutinins were like-

wise not illuminating. A 2-fold rise from an initial titer of 1:20 was demonstrated in two of these patients. Serial specimens of serum in the six remaining patients showed either no agglutinins for the strain of Streptococcus MG that was used or the same low titers (1:20 or less) in all specimens and could be considered as probably not significant.

patients with primary atypical pneumonia that were included in Groups I and II.

MISCELLANEOUS CASES WITH COLD AGGLUTININS

The nine remaining patients, in each of whom cold agglutinins were demonstrated in significant or in rising titers, form a rather

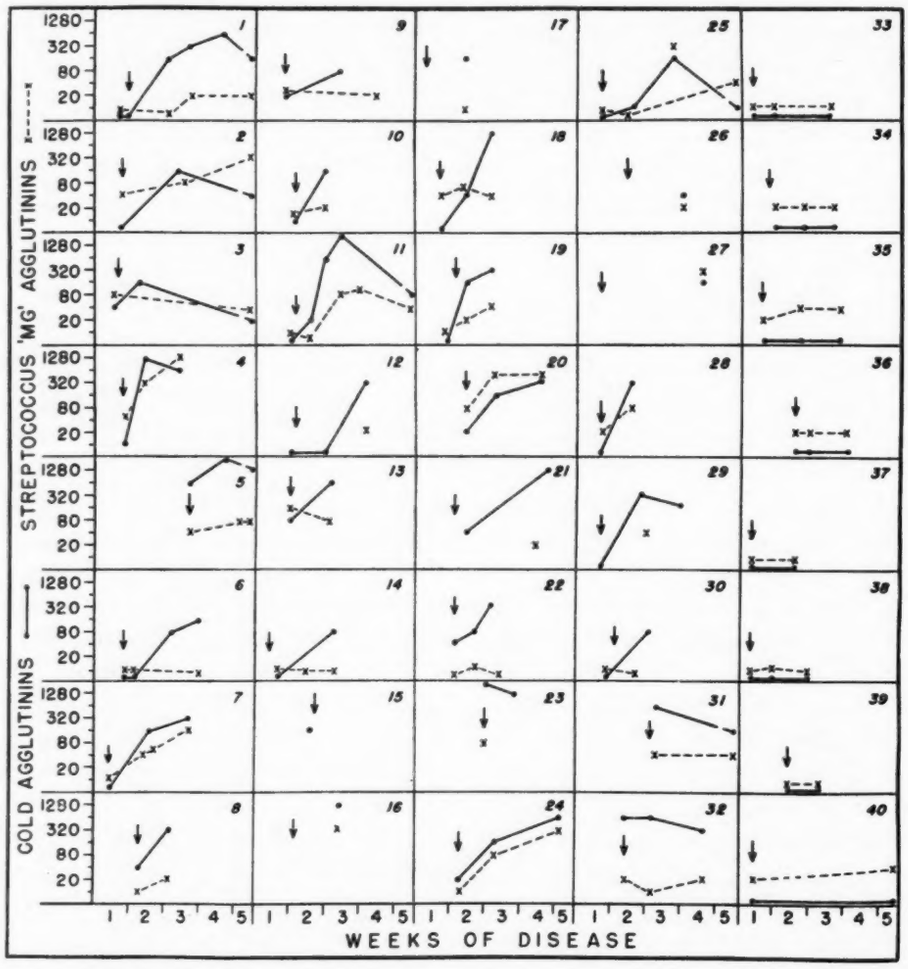


FIG. 5. Results of tests for cold agglutinins and for Streptococcus MG agglutinins in forty patients with primary atypical pneumonia who were treated with aureomycin. The arrows indicate the time when aureomycin was started.

The results of all of the tests for cold agglutinins and for Streptococcus MG agglutinins done in each of the forty patients of Groups I and II are charted in Figure 5.

Tests for Psittacosis, Q Fever and Influenza. The complement fixation tests for psittacosis and Q fever and the antihemagglutination tests for influenza A and B yielded no significant titers or changes in titers of antibodies for these agents in any of the forty

heterogeneous group. The clinical manifestations and the response of these patients to aureomycin therapy varied considerably. The relevant bacteriologic and serologic findings in these cases are shown in Table VI. The significant diagnoses finally arrived at, together with a resumé of the therapy used and an evaluation of the response in each case are given in Table VII. For the sake of brevity only a few comments will be made

concerning some of the features of these cases as a group and the highlights of the more interesting cases will be presented.

It may be pointed out in passing that the sex and age distribution of these cases was in sharp contrast to that noted for the agglutinins. Furthermore, six of these patients had received penicillin either alone or with sulfadiazine without any evidence of beneficial effect. The physical and roentgenographic findings in the lungs, however, were consistent with the final diagnoses as

TABLE VI

RELEVANT BACTERIOLOGIC AND SEROLOGIC FINDINGS IN NINE PATIENTS IN WHOM THE DIAGNOSIS OF PRIMARY ATYPICAL PNEUMONIA WAS CONSIDERED

Case*	Bacteriology		Serologic Titers†						
	Blood	Sputum	Day of Disease	Cold Agglutinins	Strep. MG Agglutinins	Complement Fixation		Influenza Antihemagglutinins	
						Psittacosis	Q Fever	A (PR8)	B (Lee)
41	0	Positive for tubercle bacilli	? 6	20	20	0	0	16	16
			16	80	0	0	0	16	16
42	0	E. coli,	? 6	20	0	0	0	16	4
		B. proteus	20	80	0	0	0	16	4
43	0	Strep. viridans,	?25	160	0	—	—	8	16
		E. coli	39	160	0	—	—	4	8
44	0	—	?12	80	0	—	—	4	64
			17	40	0	—	—	4	32
45	0	H. influenzae,	?13	80	20	—	—	32	16
		B. proteus,	22	80	40	—	—	32	8
		A. aerogenes	32	40	20	—	—	16	4
46	0	Pneumococcus 3,	?15	0	0	—	—	8	16
		H. influenzae,	18	10	0	—	—	—	—
		B. proteus	25	40	0	—	—	128	8
			51	40	0	—	—	64	8
47	0	Pneumococcus 33	?15	640	0	0	0	8	4
			28	640	0	0	0	8	4
			53	640	0	0	0	4	4
48‡	0	Strep. viridans,	15	160	0	0	0	16	8
		E. coli	20	40	0	0	0	16	4
			39	40	0	0	0	16	4
49	0	H. influenzae,	13	5120	40	0	0	8	4
		A. aerogenes, Ps. aeruginosa	21	5120	160	0	0	8	4

* The course and other relevant findings in Case Nos. 46, 47 and 48 are shown in Figures 6, 7 and 8, respectively.

† The titers are expressed as reciprocals of the final dilution of serum. 0 = negative in the lowest dilutions tested; — = not done.

‡ This patient had a marked rise in heterophile antibodies. (Fig. 8.)

patients in Group I and II and is comparable to that seen among bacterial pneumonias in this hospital. All but one of the patients in Group III were males and seven of the nine were over fifty years old.

The diagnosis of viral pneumonia was considered in the present cases in part because of the clinical findings and, in retrospect, because of the demonstration of cold agglutinins. Furthermore, six of these patients had received penicillin either alone or with sulfadiazine without any evidence of beneficial effect. The physical and roentgenographic findings in the lungs, however, were consistent with the final diagnoses as shown in Table VII, although in Cases 48 and 49 and in parts of the involved lungs in Cases 46 and 47 these findings were indistinguishable from those of primary atypical pneumonia. The possibility cannot be excluded that primary atypical pneumonia had played a role in any of these patients and may have accounted for the development of the cold agglutinins or their

presence in significant titers in the first specimens of serum that were available. This possibility is particularly difficult to exclude because of the indefinite onset and the long duration of symptoms prior to admission in most of these patients. It seems unlikely, however, that this disease played a major role in the course of the illness at the time aureomycin therapy was started except possibly in Case 49.

TABLE VII

FINAL DIAGNOSES WITH A RESUMÉ OF AUREOMYCIN TREATMENT AND ITS EFFECTS IN NINE PATIENTS IN WHOM THE DIAGNOSIS OF PRIMARY ATYPICAL PNEUMONIA WAS CONSIDERED

Patient	Sex	Age	Final Diagnoses	Severity of Respiratory Symptoms	Previous Therapy		Aureomycin Therapy*			
					Agent	Days	Day Begun	Total Dose		Estimated Benefit
								Gm.	Days	
41	M	27	Pulmonary tuberculosis; malaria; thrombophlebitis and pulmonary embolism (post-appendectomy)	Moderate	None	..	? 6 10	3 8	1 2	None
42	M	51	Fractured hip; pulmonary infarction and atelectasis; auricular fibrillation; alcoholism	Moderate	Penicillin	2	? 8	26	6	None
43	M	59	Pulmonary atelectasis (postoperative); perforated peptic ulcer; peritonitis	Severe	Penicillin Sulfadiazine	5 3	?23	32 i.m., 2.1	10 4	None
44	M	79	Cardiac failure, bronchopneumonia (etiology not determined); herpes simplex	Severe	Sulfadiazine Penicillin	4	10	10	3	Slight
45	M	57	Acute and chronic bronchitis; bronchiectasis	Moderate	Penicillin	10	?20	29	10	Moderate
46†	M	65	Influenza A; mixed bacterial (Pneumococcus 3 and H. influenzae) pneumonia	Severe	None	..	?15	i.m., 2.5 5.5	5 4	Good
47‡	F	58	Pneumococcal bronchopneumonia; bronchial asthma; eosinophilia	Moderate	None	..	?14	13.5	3	Good
48§	M	33	Infectious mononucleosis with hepatitis and atypical, non-bacterial pneumonia	Severe	Penicillin	5	15	19	6	Moderate
49	M	52	Raynaud's disease; cardiac failure; ? coronary thrombosis; ? primary atypical pneumonia	Critical	Penicillin	? 3	? 9 15 22	? 2 4 12	1 2 3	? Slight, temporary, died

* Orally except in Patient 43 who received most of the antibiotic by stomach tube and some intramuscularly, and in Patient 46 who also received some intramuscularly.

† See Figure 6. ‡ See Figure 7. § See Figure 8.

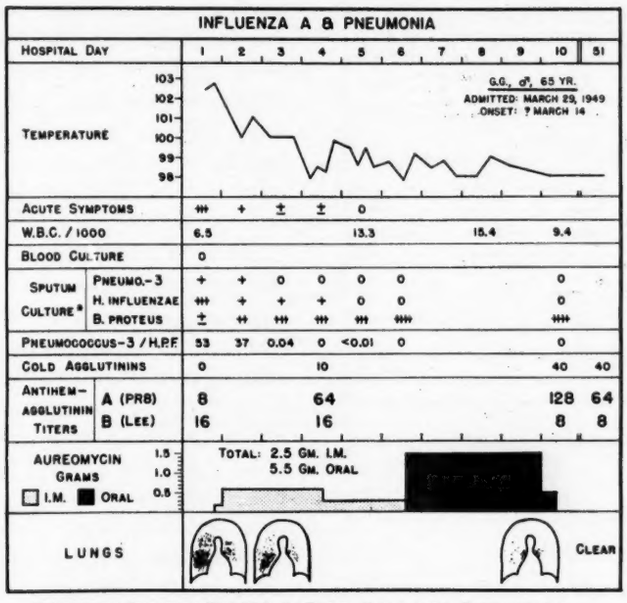
The first three patients in this group showed little or no benefit from aureomycin and the fever and symptoms either persisted for several days or relapsed during aureomycin therapy. The illness in Case 44 began with mild coryza and slight fever, headache and malaise all of which subsided completely within thirty-six hours under sulfadiazine therapy. After four days the patient again developed fever, up to 102°F., associated with moderate substernal oppression and dyspnea. He had developed herpes labialis* and was now found to have auricular fibrillation and diffuse rales in both lung bases. He was given sulfadiazine and penicillin without effect and then was digitalized and started on aureomycin. At that time the rales in his lungs had become more extensive and a roentgenogram showed patchy consolidation in the lower lobes in addition to diffuse fine mottling and there was an area of atelectasis in the left lower lobe. His leukocyte count was 12,000 of which 92 per cent were polymorphonuclears. The patient's temperature dropped and symptoms improved gradually over a period of four days. There was no sputum available for bacteriologic examination. The significance of the cold agglutinins in this case is not clear and the benefit from aureomycin if any was slight.

In Case 45 the patient had a productive cough and fever with temporary improvement from penicillin. Aureomycin was started at the end of the fourth week during a relapse of fever and dyspnea and while the patient was receiving 100,000 units of penicillin intramuscularly every two hours. At that time there were diffuse sonorous and bubbling rales at both lung bases and the white blood count was 20,000. A profuse growth of H. influenzae was obtained from the sputum. The patient's symptoms improved markedly within twenty-four hours after aureomycin was started and the temperature dropped

* Herpes simplex has very rarely been seen in characteristic cases of primary atypical pneumonia in this hospital or in the cases reported in the literature.

gradually over a period of three days. A less profuse growth of H. influenzae was obtained from the sputum culture again two days later but subsequent cultures yielded only B. proteus and Aerobacter aerogenes.

The remaining four patients are of particular interest because their clinical manifestations more closely resembled those characteristic of primary atypical pneumonia. In three of these patients the clinical and radiographic findings and the course of the illness could be adequately explained on the basis of other diseases for which the diagnostic criteria were satisfied.



* AUREOMYCIN SENSITIVITY (MCG/ML): PN. 3 = 0.78, H. INFL. = 0.78, B. PROTEUS = 200

FIG. 6. Case 46.

Case 46. This patient's illness began two weeks before admission with slight coryza and frontal headache associated with general muscle aching. He had several shaking chills during the first two days and postocular pain, photophobia and vomiting for four days. After a week he developed a cough which later became productive of scant, mucoid and occasionally blood-streaked sputum. At the time of entry to the hospital he was acutely ill and dyspneic and examination revealed some pharyngeal injection, dullness and increased breath sounds over part of the right lower lobe and coarse crepitant rales over most of the right lung and at the left base. He had received no previous therapy. The course and relevant findings in this patient are charted in Figure 6. Because he had been vomiting and because of special interests at that time, treatment was started with intramuscular aureomycin in doses of 100 mg. every four hours. The patient's symptoms improved rapidly and his temperature dropped slowly but steadily.

This patient's illness occurred during a period when influenza was known to be prevalent in the community and the diagnosis of influenza A was established in his case by the demonstration of a specific and marked rise in titer of antibodies for that virus. Type 3 pneumococci in large numbers were identified directly in his sputum and a profuse growth of H. influenzae was obtained, in addition, in the sputum cultures. Cold agglutinins also developed in this patient's serum but the titer never exceeded 1:40, which was lower than the maximum titers obtained by the same method in the characteristic cases of primary atypical pneumonia of Group 1 and agglutinins for Streptococcus MG were not found. The possibility of a co-existing infection of this type, however, cannot be entirely dismissed.

Case 47. This was a patient with a history of recurrent asthma over many years who two weeks before entering the hospital began to have malaise, weakness, a dry, hacking cough and substernal congestion which made her breathing difficult and which limited but did not entirely interfere with her work as a waitress. The symptoms continued over a period of nine days during which her appetite decreased, the dyspnea and "wheezing in her chest" increased

and she began to raise purulent sputum. When first seen she was acutely ill with marked dyspnea, wheezing and cyanosis and she was raising mucopurulent sputum. There was diminished resonance over both lung bases with an area of definite dullness on the right and musical

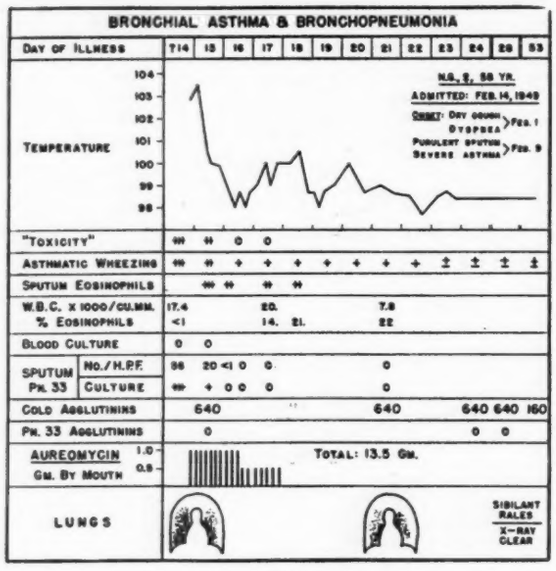


FIG. 7. Case 47.

and crepitant rales throughout both lungs. The course, therapy and other significant data are shown in Figure 7. There was a prompt drop in temperature and marked subjective improvement after the first day of aureomycin treatment. Breathing became much easier at that time but some wheezing continued throughout the next few weeks and was only temporarily and partly relieved by bronchodilator drugs and by sedatives.

Of interest in this patient was the blood eosinophilia and the finding in the sputum of large numbers of eosinophils which were estimated at from 10 to 15 per cent of all the cells that could be identified. The blood eosinophilia was not present before aureomycin was started but unfortunately the cytology of the sputum was not studied until the following day when cosinophils were found in abundance. Cold agglutinins were demonstrated in the serum in high titer at this time. Type 33 pneumococci were found in pure culture in the sputum and rapidly disappeared after aureomycin therapy. This patient's illness may, therefore, have started as a primary atypical pneumonia but the findings other than the cold agglutinins were entirely consistent with bronchial asthma complicated by a pneumococcal bronchopulmonary infection and the so-called Loeffler's eosinophilic infiltration of the lung.

Case 48. At the time of admission to the hospital this patient had a fully developed clinical picture of infectious mononucleosis with marked enlargement of the liver, spleen, tonsils and many lymph nodes and evidence of impairment of hepatic function. He had a cough since the onset and at the time of entry a few rales were heard at the lung bases and fine nodular densities extending out from both lung roots were seen in the roentgenograms. Some of the highlights of the course, therapy and laboratory data in this case are shown in Figure 8. There was no effect from penicillin which had been given at home and also during the first week in the hospital while the lesion in the lungs was extending. After aureomycin was started there was a gradual and steady drop in temperature with general improvement in all symptoms including the cough and sore throat both of which cleared completely by the third day.

In this patient, too, the pulmonary signs and symptoms may have been due to a coincidental primary atypical pneumonia which could account for the finding of cold agglutinins in moderately high titer by the end of the second week and the subsequent drop in this titer. On the other hand, similar pulmonary findings have been described in some cases of infectious mononucleosis.[12–14] The response of the latter disease to aureomycin has not yet been fully elucidated and the relation of aureomycin therapy to the improvement of this patient may have been only coincidental.

Case 49 is of particular interest. This patient was known to have Raynaud's disease for many years and over the course of the fifteen years preceding the immediate illness he had had a left, mid-thigh amputation and amputations of the distal phalanges of almost all his fingers. On January 28, 1949, the patient developed a "head cold," felt drowsy and began to cough and raise some mucopurulent sputum. During the next few days he had alternating chills and fever and at least one frank chill after which his temperature rose to 102°F. He then developed marked weakness with progressively increasing dyspnea and orthopnea. His physician treated him with sulfonamides and penicillin and when these did not seem to have any effect he gave him aureomycin. His temperature then dropped but because of nausea and vomiting the aureomycin was stopped after only a few doses. The fever

promptly returned and he was admitted to the hospital on February 10th.

At that time he appeared severely ill, moderately cyanotic, dyspneic and orthopneic; the temperature was 99.4°F., pulse 110, respirations 36 and blood pressure 180/100. Scattered moist

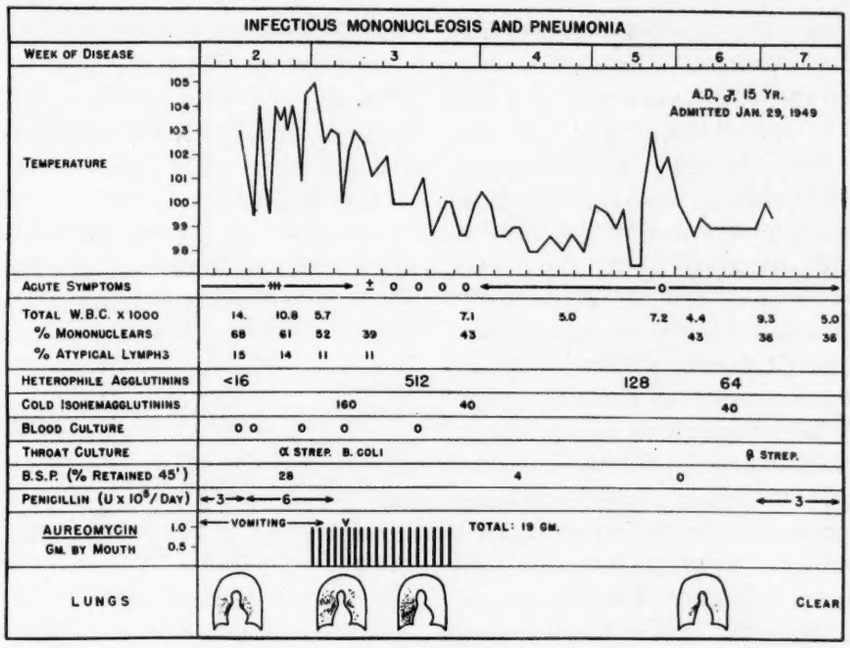


FIG. 8. Case 48.

rales and rhonchi were heard throughout both lungs; the heart was slightly enlarged, the liver edge was felt 7 cm. below the costal margin and the abdomen was moderately distended. Roentgenograms showed finely mottled infiltrations extending radially from both hilar regions, somewhat more extensively on the right. The white blood count was 11,300 of which 72 per cent were polymorphonuclears. An ECG showed sinus rhythm, rate of 103, PR .20, QS .09, deep Q_3 and normal axis and these findings were interpreted as indicating myocardial disease.

The course in the hospital was characterized by increasing dyspnea, orthopnea, cyanosis and tightness in the chest with only a few days of partial remission from the symptoms shortly after entry and after the patient was digitalized. There was only slight benefit from oxygen and from bronchodilator drugs except during this remission. The blood pressure dropped during the first few days to 145/65. There was profuse sweating and the extremities were cold and cyanotic. The signs in the lungs cleared slightly by x-ray during the first few days but the rales persisted unchanged throughout both lungs. There were also three short bouts of low grade fever; in the first the maximum temperature was 100°F. and this subsided during aureomycin administration; in the second the daily fluctuations varied but the maximum did not exceed 101°F. and there was no effect from aureomycin; the final episode in which the temperature did not exceed 101°F. lasted five days until the patient died on March 1.

The exact cause of death in this patient was not determined since permission for autopsy was denied. The high titer of cold agglutinins in the serum (Table VI) at the time of admission may have been associated with primary atypical pneumonia that began two weeks previously and this may have improved slightly during the first two courses of aureomycin but later progressed when this antibiotic was stopped. Alternatively, and what seemed more likely at the time when the patient was being observed, the high titer of cold agglutinins was associated with the chronic vascular disease and the respiratory symptoms were due to involvement of the coronary vessels that resulted in cardiac failure. Unfortunately, a decisive answer cannot be given. If this patient's death was indeed the result of a primary pneumonia, and the rise in titer of agglutinins for Streptococcus MG lends some support to this possibility, this case must be considered as representing a failure from aureomycin therapy and that failure might then be attributable either to improper administration of the antibiotic or to concurrent cardio-

vascular disease. On the other hand the entire picture may be considered to be the result of the vascular disease associated with cold agglutinins,[15–17] this disease having been activated or aggravated by some acute respiratory infection.

Summarizing the results of aureomycin therapy in the nine cases of Group III, it is evident that there was no effect in the first three patients whose pulmonary lesions were not related to primary atypical pneumonia or to any significant acute bacterial infection. In each of the four patients in whom primary atypical pneumonia may possibly have been a factor early in the disease but pneumococcal or mixed bacterial infections probably played a significant if not a major role at the time when aureomycin was started, there was a definite though variable beneficial effect. The case with atypical pneumonia accompanying infectious mononucleosis seemed to improve under aureomycin therapy but this may have been coincidental. Finally, in the patient with Raynaud's disease the fatal illness was either a primary atypical pneumonia in which partial and temporary improvement occurred during brief and inadequate courses of aureomycin but the general course of the illness was not affected because of the severe underlying cardiovascular disturbance; or the major illness was part of the patient's underlying disease and some respiratory infection, possibly primary atypical pneumonia, was only incidental in the course of the final episode.

UNTOWARD EFFECTS

The only untoward reactions from the oral doses of aureomycin were limited to gastrointestinal symptoms. There was some vomiting in one-half of the patients and in six others there was nausea without vomiting. These symptoms were mild or moderate in most cases and did not interfere with adequate dosage but in a few patients they were severe enough to necessitate either omission of some doses or reduction in their size, and in four cases the drug was discontinued because it could not be tolerated. Frequent bowel movements that were bulky and soft were noted in eight patients, including five who had some nausea or vomiting. In thirteen of the forty-eight patients there were no gastrointestinal symptoms from full oral doses. The intramuscular injections gave considerable local pain and tenderness even when procaine was used but no ill effects resulted from the intravenous injections. There was no clinical or laboratory evidence of any toxic effects on the blood, kidneys, liver or nervous system that could be attributable to aureomycin. Fever or rashes definitely ascribable to the aureomycin were not observed in any of the 49 patients in this study.

COMMENT

In the absence of evidence to the contrary it has been accepted as a major premise that, like the sulfonamides and like other effective antibiotics, aureomycin exerts its beneficial effects in various infections by antimicrobial action against the etiologic agents. In the case of most infections in which the etiologic agents can be identified adequate evidence for this premise can be adduced. This cannot, however, be done in cases of primary atypical pneumonia in which the causative agent has eluded specific identification.

In searching for criteria for the selection of cases to include in the category of "viral" or primary atypical pneumonia for the purpose of evaluating therapy, reliance has been placed on three features: (1) the characteristic clinical findings, including the symptoms, physical signs, roentgenograms, leukocyte counts, etc.; (2) the exclusion of other possible or likely causative agents, as far as feasible, through bacteriologic and serologic studies and (3) the development of cold agglutinins in high titer or their occurrence in significant titers at the proper stage of the illness, namely, on or after the middle of the second week of symptoms.

In this laboratory the cold agglutinin test has proved to be the most useful one in segregating a homogeneous group of cases

from among acute respiratory infections which are associated with characteristic pulmonary lesions and in which no definite etiologic agents could be established. It is for that reason that the patients included in this study have been divided into three groups. Those in Group I satisfied all three criteria and thus represent as nearly a homogeneous group as could possibly be selected at the present time. The patients in Group II were similar in every respect but cold agglutinins could not be demonstrated. The agglutination tests with Streptococcus MG did not seem to offer any further aid in the classification of the present cases. In fact, significant rises in titer of agglutinins for the strain used were less frequent and did not appear to be so definitive as those for cold agglutinins.

It should be noted that the cases included here represent only a part, though a highly important one, of the cases of acute respiratory infections in which the therapeutic value of aureomycin was investigated. While most of the patients in Groups I and II were treated with aureomycin deliberately because the diagnosis of "viral" pneumonia was considered to be the most likely one at the time, their final inclusion in this series was based on all the accumulated evidence. In a significant number of other cases in which the diagnosis of primary atypical pneumonia was at first seriously considered, further evidence resulted in their inclusion in other diagnostic groups which are presented elsewhere.

The evidence for the beneficial effect of aureomycin on the course of the disease in the present cases of primary atypical pneumonia, if not entirely conclusive, is nevertheless quite convincing. In the patients of both Group I and Group II there was a sharp drop in temperature and definite and marked improvement in the acute symptoms in direct response to the administration of the antibiotic. Irregular or incomplete responses were rare and even then were generally associated with inadequate dosage or premature discontinuance of therapy. Furthermore, essentially similar beneficial effects were noted in the patients in whom treatment was begun early in the disease and in those in whom aureomycin was started after the first week. In some of the latter, of course, the clinical improvement that followed exhibition of the drug may have been coincidental. The fact that this number of consecutive cases showed similar responses, however, can hardly be ascribed to coincidence. When considered together with the equally favorable responses already reported,[2,3,4] it must be concluded that aureomycin is a highly effective agent in primary atypical pneumonia.

The role of aureomycin in the heterogeneous cases of Group III has already been discussed. The results in these cases serve to emphasize both the versatility and the limitations of aureomycin. On the other hand, if the initial major premise, namely, that antibiotics exert their major curative effects on the microbial incitants of disease, is correct, the uniformly favorable effects of aureomycin in cases of primary atypical pneumonia should stimulate further efforts to identify the causative agent or agents of this disease.

The optimum dosage was not determined. However, a total dose of between 10 and 15 gm. given over a period of three to four days appeared to be adequate in almost all of the cases in Groups I and II. Since many of the lots of aureomycin used in this study produced nausea and vomiting quite frequently, it was sometimes necessary to reduce the size of the individual doses or to increase the interval between doses. This did not usually affect the favorable course unless too long an interval was allowed to elapse without treatment or when aureomycin was started very early in the course of the disease. Alternative dosage schedules currently recommended for therapy are: 1 gm. every four or six hours, or 0.5 gm. every three or four hours in average adults. Such dosage may be continued until the temperature reaches essentially normal levels and the acute symptoms have been relieved. After that, doses of 0.5 gm. every four or six hours may be given for one to four more

days, the longer period of treatment being reserved for those who show a slow or incomplete response.

SUMMARY AND CONCLUSIONS

Aureomycin produced a prompt and marked beneficial effect on the fever and symptoms in each of forty patients with the characteristic finding of so-called viral or primary atypical pneumonia. Cold agglutinins were demonstrated in the serum of thirty-two of these patients in significant or in rising titer on or after the middle of the second week of the disease.

In a group of nine additional patients in whom cold agglutinins were demonstrated but in whom the pulmonary findings were accounted for on the basis of diseases other than primary atypical pneumonia, the response to aureomycin was variable. The possible role of primary atypical pneumonia in this group of patients was discussed.

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Aureomycin in the Treatment of Influenza and Certain Other Acute Respiratory Infections with or without Pneumonia*

MAXWELL FINLAND, M.D., E. BUIST WELLS, M.D., HARVEY S. COLLINS, M.D. *and* THOMAS M. GOCKE, M.D.

Boston, Massachusetts

THE versatility of aureomycin as an antibiotic[1] encompasses a wider variety of known bacterial and nonbacterial causative agents of pneumonia than any of its effective predecessors, including penicillin and streptomycin. Aureomycin also appears to be effective in primary atypical pneumonia of unknown etiology, the so-called virus pneumonia.[2–5] It seemed, therefore, to be eminently suitable for extensive clinical trials in the treatment of pneumonias of diverse etiology. The results of clinical and laboratory studies in several different etiologic groups of pneumonias in which the value of aureomycin therapy was investigated have been presented in other communications.[6–8] The present report deals with similar studies in a heterogeneous group of forty-one patients treated with aureomycin. Included are some proved cases of influenza A, with or without pneumonia, cases of other simple respiratory tract infections and a few pneumonias in which a significant etiologic agent could not be determined but which did not satisfy the usual clinical criteria for the diagnosis of primary atypical (virus) pneumonia.

MATERIALS AND METHODS

Selection of Cases. The patients were all adults from the medical wards of the Boston City Hospital except for a few who were treated in nearby hospitals or at home. At the time when treatment with aureomycin was started, they were all febrile and acutely ill and either had definite signs and symptoms of pneumonia or they appeared severely ill with acute respiratory symptoms but without definite evidence of pneumonia. For the purpose of this presentation the patients have been divided into three groups based on all of the available clinical and laboratory findings.

Group I includes eighteen patients in whom a diagnosis of influenza A was established by serologic test and in a few instances an influenza virus was isolated from pharyngeal washings obtained during the acute phase of the disease and before any aureomycin was given. Most of these patients also had clinical evidence of pulmonary involvement but this was demonstrable by roentgenograms in only seven of them and in none of the latter was any significant bacterial pathogen identified in cultures of blood or sputum obtained during the acute stage of the disease.*

Group II includes ten patients who had clinical findings similar to those of Group I. Serologic tests in these patients, however, all yielded negative results. In particular, they failed to demonstrate any diagnostic titers or rises in titers of cold agglutinins or influenza antibodies, and the attempts made to isolate influenza viruses from the pharyngeal washings of some of them likewise all failed. Roentgenograms failed to show any pulmonary involvement in any of these ten patients.

* Patients with proved influenza virus infection who had pneumonia which was revealed by x-ray and, in addition, pneumococci or other significant pathogenic bacteria are considered in the other papers.[7,8]

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services, Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass. Aided by a grant from the United States Public Health Service.

Group III includes thirteen patients all of whom had definite signs of pulmonary consolidation by physical examination and in x-ray films. In all of these patients cultures of blood and sputum failed to yield any significant respiratory pathogens and serologic tests were entirely negative.

TABLE I
DISTRIBUTION BY AGE AND SEX IN THREE GROUPS OF PATIENTS WITH RESPIRATORY INFECTIONS TREATED WITH AUREOMYCIN—1948–1949

Distribution	No. of Patients		
	Group I	Group II	Group III
Sex:			
Males	6	7	7
Females	12	3	6
Age:			
29 years or less	9	3	
30–49 years	6	6	6
50 years or older	3	1	7

The distribution by sex and age of the patients of these 3 groups is shown in Table I.

Other antimicrobial therapy, either penicillin or sulfadiazine, had been used for from three to seven days in three of the patients in Group I and in two of those in Group III. In each of these five patients there was no improvement and the fever and symptoms progressed during treatment with these agents.

Bacteriologic Studies. Cultures of blood and sputum (or of pharyngeal swabbings when sputum could not be obtained) were made before aureomycin was started and sputum or throat cultures were usually repeated on several occasions during and after treatment. The sputum and pharyngeal cultures were planted routinely in blood broth and on the surface of blood agar plates. Smears of the sputum were examined in gram-stained preparations and by the Neufeld method.

Serologic Studies. These included tests for cold agglutinins, Streptococcus MG agglutinins, antibodies for influenza A and B and, in a few cases, also complement fixing antibodies for psittacosis and Q fever. The methods were similar to those used in the other parallel studies.[6]

Isolation of Influenza Virus. Throat washings from selected cases were collected in sterile skimmed milk or in 10 per cent horse serum broth, sealed in pyrex capsules, quickly frozen and stored in a dry ice storage box until used. The methods employed in attempts to isolate influenza viruses from these washings are similar to those used in previous studies.[9]

TABLE II
ANALYSIS OF DOSAGE

Dosage	No. of Patients		
	Group I	Group II	Group III*
Starting schedule by mouth:			
1.0 gm. every 4 hr	3	..	5
1.0 gm. every 6 hr	7	..	4
0.5 gm. every 4 hr	6	7	1
0.5 gm. every 6 hr	2	3	2
Total oral dose:			
Less than 10 gm	7	5	2
10–14 gm	6	3	5
15–19 gm	3	..	3
20 gm. or more	2	2	2
Average (gm.)	(11.9)	(10.4)	(13.4)
Interval, first to last oral dose:			
48 hours or less	3	2	3
49–72 hr	5	3	2
73–96 hr	4	4	1
97–120 hr	3	..	1
6–10 days	3	1	5
Average (days)	(3.8)	(3.4)	(4.6)

* Intravenous therapy alone was used in Case 32; 3 doses of 500 mg. and 1 of 250 mg. at twenty-four-hour intervals; total 1.75 gm.

Parenteral therapy was used in addition to the oral doses, as follows:

Case 38. 100 mg. intramuscularly at three-hour intervals; total 0.3 gm.

Case 40. 500 mg. intravenously at twenty-four-hour intervals; total 1.5 gm.

Case 41. 100 mg. intramuscularly at four-hour intervals; total 2.0 gm.

Dosage. An analysis of the dosage used in all of the patients is shown in Table II. Almost all of the aureomycin* was given by mouth in doses of 1.0 or 0.5 gm. each at intervals of four or six hours. These doses were reduced or the intervals lengthened in many of the patients after their temperatures reached normal and their conditions improved. For all of the patients in the three groups the average total dose by mouth was about 12 gm. given in four days. Some of the patients in Group III were treated with larger total doses and over longer periods

* The aureomycin was provided by the Lederle Laboratories.

than those used in the other two groups. Three of the patients in Group III also received some parenteral doses to supplement those given by mouth and one patient received all of the aureomycin intravenously. The intramuscular doses, which were used in only two patients, were given every three or four hours in the form of a glycinate of aureomycin in 100 mg. amounts, each in a volume of 5 cc. of physiologic saline. For each of the intravenous doses either 500 or 250 mg. of aureomycin hydrochloride were given in 1,000 or 1,500 cc. of physiologic saline or dextrose solution and allowed to run in slowly, usually over a period of an hour or more.

TABLE III

RELEVANT FINDINGS IN EIGHTEEN PATIENTS WITH INFLUENZA A AND BRONCHOPULMONARY INVOLVEMENT WHO WERE TREATED WITH AUREOMYCIN BY MOUTH (1949)

Patient	Sex	Age	Date of Onset	Status When Aureomycin Was Started*					Influenza Antihemagglutinins‡	
				Day of Disease†	Lung Findings	Tem. °F.	W.B.C.	Severity of Symptoms	A (PR8)	B (Lee)
1	F	21	Feb. 1	4	Tracheobronchitis	102.	8,200	Moderate	8/32	8/8
2	M	25	Feb. 3	3	Tracheobronchitis§	103.4	5,600	Moderate	4/64	4/4
3	F	14	Feb. 20	11 (4)	Atypical pneumonia	104.8	11,000	Moderate	128/128	4/4
4	M	16	Feb. 20	16 (8)	Tracheobronchitis	102.	9,600	Moderate	128/256	16/16
5	M	13	Feb. 27	2	Tracheobronchitis	103.	5,000	Severe	0#/32	0/0
6	F	24	Mar. 4	2	Tracheobronchitis	103.	6,700	Moderate	0#/4	0/0
7	F	68	Mar. 5	5	Atypical pneumonia	102.4	9,500	Severe	8/128	32/16
8	F	42	Mar. 11	4	Atypical pneumonia	102.	6,700	Moderate	0/16	4/4
9	F	21	Mar. 13	3	Tracheobronchitis§	103.8	7,000	Mild	16/64	8/8
10	F	40	Mar. 16	3	Tracheobronchitis	102.	4,700	Moderate	0/8	4/0
11	M	33	Mar. 17	3	Tracheobronchitis	103.	7,000	Moderate	0#/16	4/4
12	F	73	Mar. 17	4	Tracheobronchitis	103.8	3,900	Severe	4/16	4/4
13	F	21	Mar. 20	2	Tracheobronchitis	104.	10,000	Moderate	16#/128	0/0
14	F	48	Mar. 21	8	Atypical pneumonia	102.	9,000	Moderate	—/512	—/8
15	F	72	Mar. 21	3	Atypical pneumonia	102.6	11,000	Moderate	0#/32	16/16
16	M	21	Mar. 22	7	Tracheobronchitis	105.	13,100	Moderate	8/32	16/16
17	M	34	Mar. 30	4	Lobar pneumonia	101.	19,600	Severe	0/128	4/16
18	F	33	Apr. 1	5	Atypical pneumonia	102.	10,500	Mild	4/32	16/16

* The predominant organism in pharyngeal or sputum cultures was Streptococcus hemolyticus in Cases 1, 2, 4, 5 and 16 and Staphylococcus aureus in Cases 6 and 12. No significant pathogens were obtained from the cultures of the remaining cases. Blood cultures showed no growth in every case. Penicillin had been given for three days before aureomycin was started in Cases 7, 10 and 14.

† The number in parenthesis indicates the number of days after supposed onset of pneumonia; other figures indicate number of days after onset of clinical influenza.

‡ The titers (acute/convalescent) are given as the reciprocals of the final serum dilutions; 0 = < 1:4; — = not done; # = influenza virus isolated.

§ Lungs essentially clear except for musical rales by physical examination; in all of the remaining patients the physical signs were consistent with atypical pneumonia, but only those in whom x-rays also showed lesions consistent with that diagnosis are listed as such.

RESULTS IN PATIENTS WITH INFLUENZA

Some of the relevant findings in the eighteen patients included in Group I are listed in Table III. The inclusion of patients in this group was based on the demonstration of a diagnostic rise in titer of antibodies for influenza A virus and in five of these patients such a virus was also isolated from garglings by inoculation of embryonated hens' eggs. In two patients in whom the initial or only blood was obtained more than seven days after the first symptoms of influenza, the titers of influenza A antibodies were high (1:128 in one and 1:512 in the other) and may be considered diagnostic. All other serologic tests were negative in each of these patients. These eighteen cases occurred during a period of prevalence of influenza that reached its peak in and around Boston during the second and third weeks of March, 1949.

Status When Aureomycin Was Started. At the time when the first dose of aureomycin was given these patients all appeared

acutely ill with symptoms and other findings which in most respects resembled those of primary atypical pneumonia. They had the characteristic findings of clinical influenza, namely, chilly sensations, malaise and prostration, generalized muscle aching, soreness of the eyes with conjunctival injection and slight sore throat. In addition, all of these patients also had moderately severe cough which was sometimes productive of small amounts of blood-tinged mucoid sputum and they complained of substernal soreness. In a few the onset was with a severe shaking chill. Some of the patients were slightly to moderately dyspneic and cyanotic.

Duration of Illness. Most of the patients were first treated with aureomycin on or before the fourth day of their illness. In patients 3 and 4, in whom treatment was started on the eighth and eleventh day, respectively, after the onset of the influenza, there had been a complete remission of symptoms for several days. Chills, fever and acute symptoms recurred with increased severity four days before aureomycin was started in the former and eight days previously in the latter. Several other patients had also had a brief but only partial remission of symptoms earlier.

Fever and Leukocyte Counts. The temperature at the time when the first dose of aureomycin was given ranged from 102° to 105°F., except in one patient in whom it was 101°F. The white blood counts were essentially normal except in three patients in whom they were slightly elevated and in one, patient 17, in whom it was 19,600.

Pulmonary Involvement. The findings in the lungs were consistent with tracheobronchitis or atypical pneumonia. Under the former designation, as listed in Table III, are included those in whom there were diffuse musical rales and, except in two patients, there were also numerous crepitant rales, usually limited to one or both lung bases. Roentgenograms in these cases, however, showed only increased bronchial markings without any areas of increased density in the lung parenchyma. In those listed as atypical pneumonia the physical signs were essentially the same except that crepitant rales were more prominent, there was slight dullness over some part of the lungs and the x-ray films in all these patients showed areas of soft, mottled densities similar to those usually seen in cases of primary atypical pneumonia. In Case 17 there were physical signs and x-ray findings of consolidation with some atelectasis of the right lower lobe.

Bacteriologic Findings. All of the blood cultures taken in these patients yielded no growth. In those patients who were listed as having atypical pneumonia no significant pathogens were identified in any of the cultures of the sputum or pharyngeal swabs. The growth in these cultures was usually scant and Streptococcus viridans and/or Neisseria catarrhalis usually predominated. However, among those who showed no intrapulmonary lesions by x-ray and who are listed in Table III as having tracheobronchitis, these cultures yielded a predominant growth of hemolytic streptococci in five cases and of hemolytic staphylococcus aureus in two others.

Severity. The severity of the symptoms was estimated in these patients at the time aureomycin treatment was undertaken. In only two of the patients was the illness considered to be mild; in most of the others it was estimated as being of moderate severity and in four patients it was considered to be severe.

Effect of Aureomycin on Fever and Symptoms. The improvement that occurred in the clinical condition of this group of patients following the initiation of aureomycin therapy was quite striking and on the whole was either similar to or even more impressive than that which was observed in patients with pneumococcal[7] or primary atypical pneumonia.[6] There was a major and sustained drop in temperature in every case within the first thirty-six hours and in all but two of the patients this had occurred within twenty-four hours after the first dose of aureomycin. In only three of the patients did the temperature rise to 100°F.

on the third day; all of the others were entirely afebrile within forty-eight hours.

Improvement in symptoms was equally rapid. All of the major symptoms of acute illness had abated within twenty-four hours in all but two of the patients and the latter improved markedly during the second day and were free of symptoms by the end of the third day. The remaining patients were essentially symptom-free by the end of the second day. Cough persisted in four patients for periods of five to ten days but this became progressively less distressing and gradually cleared during this time.

One patient, number 5, had intense headache and signs of meningeal irritation before aureomycin was started. The cerebrospinal fluid findings at this time were those of a benign lymphocytic meningitis. This patient's fever and symptoms including the headache subsided promptly, as in the other patients, except that nausea and vomiting continued for two days. Attempts were made to isolate a virus from throat washings and spinal fluid. Influenza A virus was isolated from the former but could not be demonstrated in the latter.

Effect on Pulmonary Lesions. The rales and x-ray shadows in the lungs also cleared quite rapidly. By physical examination the lungs had entirely cleared within five to seven days in every case. X-rays showed clear lung fields in every instance in the films taken between the seventh and the ninth day after aureomycin was started. In most of the patients the lungs were entirely clear before the fifth day.

Estimation of Beneficial Effect of Aureomycin. In view of the established diagnosis of influenza in the present cases it is obviously not possible unequivocally to relate the observed improvement in these cases to the effects of aureomycin. These cases, however, do not represent "average" cases of influenza since they were selected for aureomycin therapy only because of the severity of symptoms and because pulmonary complications were already present or suspected. When judged by the marked and rapid improvement that occurred with great regularity and in direct relation to the administration of aureomycin, the beneficial effect of the antibiotic appeared to be quite impressive in all but three of these eighteen patients and even these three patients improved steadily though less rapidly after treatment was started. This improvement may, of course, have been coincidental in some of the patients but that seemed to be very unlikely in most of them. However, no parallel and comparable cases were observed without therapy or under other types of therapy so that any comparisons are not justified.

RESULTS IN OTHER ACUTE RESPIRATORY INFECTIONS WITHOUT PNEUMONIA

The ten patients included in Group II had symptoms resembling those of the patients with influenza in Group I. However, there was no roentgenographic evidence of pulmonary involvement in any of these patients and the lungs were clear to physical examination, except for some scattered musical rales heard in three of the patients. Furthermore, all of the serologic tests, including those for influenza A and B, gave entirely negative results. Inoculation of throat washings from five of these patients into embryonated hens' eggs also failed to yield any viruses. Only five of the cases in this group including one of those in which virus isolation was attempted occurred during the period when proved influenza A was prevalent.

Blood cultures in these patients were all negative. Each throat culture from two of these patients and cultures of mucopurulent sputum in a third, all obtained before aureomycin was started, yielded a predominant growth of beta hemolytic streptococci. No significant pathogens could be identified in similar cultures from the remaining patients, Streptococcus viridans and Neisseria predominating in these cultures. Pharyngitis was more prominent in the three patients from whom hemolytic streptococci were cultured than in the others, and in two of those three patients there was an exudative tonsillitis and some

cervical adenitis. The diagnosis in the remaining patients was "clinical influenza," or "undifferentiated acute respiratory disease"[10] with tracheobronchitis.

Treatment with aureomycin was started on or before the fourth day of illness in six of the patients and on the fifth or sixth day in the others. They were all acutely ill at the time and their temperatures ranged between 102° and 104.6°F. The leukocyte counts were essentially normal in half of the patients and ranged from 16,300 to 21,600 in the others. From the symptoms and general appearance of these patients the severity of their illness was characterized as mild in three and as moderate in the others. None of these patients had received any antimicrobial therapy for this illness before aureomycin was started.

In all these patients the temperature returned to normal between twelve and twenty-four hours after the first dose of aureomycin except in two who had secondary rises in temperature to 99.4°F. during the second day. Symptomatic improvement generally paralleled the drop in the temperature in each instance. In one of the patients a co-existing pyuria and E. coli bacilluria also cleared completely within two days.

The rapidity and the regularity with which aureomycin administration was followed by marked improvement in fever and symptoms in these patients strongly suggests that the antibiotic was responsible in some measure for these beneficial effects, or at least for hastening the recovery. Here again, this cannot be stated with certainty in the absence of adequate controls and since the natural evolution of the disease in these cases could not be predicted from any of the observations made at the time when the treatment was undertaken.

TABLE IV

SOME SIGNIFICANT FINDINGS IN TWELVE PATIENTS WITH PNEUMONIA IN WHOM NO ETIOLOGIC INCITANT WAS IDENTIFIED AND WHO WERE TREATED WITH AUREOMYCIN—1948–1949

Patient	Sex	Age	Predisposing Factors	Status at Time Aureomycin Was Started*					
				Day of Disease	Type of Lesion†	Lobes‡	Temp. °F.	W.B.C.	Severity of Symptoms
29	M	37	Primary	1	Lobar	Lu	103.6	29,100	Moderate
30	M	31	Primary	3	Lobar	Rml	105.	10,000	Severe
31	F	46	Primary	3	Lobar	Rml	101.8	17,600	Moderate
32	M	49	Primary	3	Lobar	Rum	101.6	25,400	Moderate
33	F	60	Primary	2	Lobar	Ll	101.4	10,000	Mild
34	M	35	Fractured ribs; alcoholism	6	Lobar	Ru	103.6	31,500	Moderate
35	M	54	Fractured ribs	9	Broncho-	Ru	102.	25,800	Moderate
36	M	76	Cardiac failure	5	Broncho-	Bilat.	105.	12,900	Severe
37	F	51	Acute rheumatoid arthritis	? 15	Broncho-	Bilat.	101.8	20,500	Moderate
38	M	75	E. coli septicemia; uremia	?	Broncho-	Bilat.	105.2	19,800	Critical
39	F	45	Cancer of cervix with metastases	5	Broncho-	Ll	103.	9,300	Moderate
40	M	73	Prostatectomy; uremia	?	Broncho-	Bilat.	103.5	16,000	Critical
41	F	83	Debility; decubitus	? 2	Broncho-	Bilat.	102.4	21,600	Critical

* Penicillin was given before aureomycin without apparent benefit for seven days in Case 35 and for five days in Case 39.

† Lobar indicates uniform density of lobar distribution and Broncho- indicates patchy areas of density in x-ray films.

‡ R = right; L = left; u = upper; m = middle; l = lower.

RESULTS IN PATIENTS WITH PNEUMONIA OF UNDETERMINED ETIOLOGY

Some of the relevant findings in the thirteen patients of Group III are listed in Table IV. This is a heterogeneous group comprising the aureomycin-treated patients with pneumonia which could not be classified etiologically. Inclusion of the patients in this group is based on the demonstration of definite areas of consolidation in the lungs by both physical examination and x-ray and the failure to identify any likely

etiologic agent, either in the cultures of blood and sputum or by any of the serologic tests employed. Furthermore, in none of these patients did the symptoms or pulmonary findings resemble those which are considered to be characteristic of so-called viral pneumonias. Clinically five of these cases were classical cases of "primary lobar pneumonia" while in each of the remaining eight the pneumonia occurred either as a complication or as a terminal event in the course of some other major illness and could be characterized in all but one instance as atypical or bronchopneumonia. These two subgroups may best be considered separately.

Patients with "Primary Lobar Pneumonia." In the first five patients the symptoms and physical and x-ray signs in the lungs could be considered as characteristic of those found in classical cases of pneumococcal lobar pneumonia but neither pneumococci nor any other significant pathogens could be identified in typical rusty sputum obtained before aureomycin treatment was started. None of these patients had received any previous therapy for this illness.

Treatment with aureomycin was started in these five patients between the first and third day of the disease. The severity of the symptoms at the time varied in the different patients, as did also the fever and leukocyte counts. Four of these patients received aureomycin entirely by mouth, the average dose being 9.5 gm. in three and one-half days. One patient, number 32, was given aureomycin only intravenously, a total of 1.75 gm. in four doses.

The response to therapy in these five patients was essentially the same as in authentic cases of pneumococcal pneumonia.[7] Fever and symptoms subsided rapidly in four of the patients. The fifth patient received only 250 mg. every six hours by mouth during the first day and showed no improvement until the following day after the individual doses were increased to 1.0 gm. The lungs were entirely clear by the ninth day in one of the patients and by the sixth day in the other four.

Patients with Pneumonia Complicating Other Conditions. In the remaining eight patients the pneumonia may be considered as "secondary" and the course and response to therapy were necessarily modified, in most of the cases, by the underlying primary disease. In two patients the pneumonia began following chest injuries in which fractured ribs were sustained. Aureomycin administration was started on the ninth day in one and on the sixth day in the other. The latter was acutely intoxicated at the time and then developed delirium tremens; the former had already received penicillin for seven days without improvement. Both of these patients were febrile and moderately ill and had high leukocyte counts when aureomycin was started. Doses of 1 gm. were given every four or six hours. There was a steady drop in temperature in each case; and although there was considerable symptomatic improvement during the first twenty-four hours, neither of these patients became afebrile or free of symptoms until the end of the third day.

In one patient, number 36, the pneumonia occurred during an episode of severe congestive heart failure and aureomycin was started on the fifth day. This patient showed marked improvement during the first thirty-six hours but complete recovery was delayed because the edema and cardiac symptoms were difficult to control.

In the remaining five patients there was only minor or temporary improvement in the fever and symptoms during aureomycin therapy and in four of these patients no additional improvement was observed when penicillin was later given in large doses, in addition. Three of these patients received parenteral as well as oral therapy. Among these five patients three (numbers 38, 40 and 41) died of their underlying disease several days after aureomycin was stopped although one of them, number 41, had improved sufficiently to be sent to a nursing home. The relation of the pneumonia to the underlying disease in the patient with acute rheumatic arthritis was a source of con-

siderable speculation. Neither the pneumonia which was rather mild and not extensive, nor the fever, nor the arthritis appeared to be influenced in the least by the aureomycin. However, in this case only 6 gm. were given over a period of two days but large doses of penicillin were later given, likewise without effect.

UNTOWARD EFFECTS

As among all other groups of patients that have been treated in this clinic, the only untoward effects that were observed from oral aureomycin were some gastrointestinal disturbances of varying severity. Among the forty patients included in the present study who received aureomycin hydrochloride by mouth, twenty had some nausea with vomiting but in most of them this was transient and was not severe enough to interfere with continuation of the therapy as planned. In a few, however, it was necessary to reduce the size of individual doses or increase the interval between doses. There were seven other patients who had only nausea but did not vomit and four patients, including two of those who had some vomiting, passed bulky, semiformed stools which in only one instance became frequent and watery. There were eleven patients who experienced none of these or any other symptoms from the oral doses.

The intramuscular doses were all accompanied by pain of varying severity which lasted up to half an hour or longer, and some local tenderness persisted for several hours. Only one of the intravenous injections was followed by a pyrogenic reaction and in a second patient there was a small localized area of cellulitis in the antecubital region where some of the aureomycin solution had extravasated. This cleared in a few days without special treatment. There were no gastrointestinal symptoms from the parenteral injections. In none of the forty-one patients was there any fever or rash, or any evidence of toxic effects on the kidney, liver, blood or nervous system that could be ascribed to the aureomycin.

COMMENT

When the sulfonamide drugs were first shown to be effective in the treatment of pneumonia, the fact that they were active against pneumonias due to all types of pneumococci and also against pneumonias caused by streptococci and some other organisms led to almost complete abandonment of bacteriologic studies in cases of pneumonia in most clinics. The importance of identifying the etiologic agent bacteriologically was re-emphasized, however, by the limitations of the sulfonamides and later, and more clearly, after it was shown that the effective action of penicillin and streptomycin is limited, in each instance, to a definite range of bacteria which, though overlapping to some extent, is nevertheless largely distinct and specific for each of these antibiotics. The effective range of aureomycin, in relation to the pneumonias, appears to be more inclusive than that of any of the earlier agents since it embraces not only the gram-positive and gram-negative respiratory pathogens but also includes the psittacosis and Q fever groups of agents.[1] Furthermore, all of the early reports on the use of aureomycin in the primary atypical or "viral" pneumonias also indicated that it is highly beneficial in such cases.[2–5] This, in turn, strongly suggests that the latter group of cases may be caused by an agent or by agents which are susceptible to this antibiotic.

The cases in the first group of this series satisfied the criteria for the diagnosis of infection with influenza A virus. Almost all of these patients had bronchopulmonary lesions recognizable clinically. Among the cases in which definite pulmonary lesions were not revealed in the roentgenograms and which have here been designated as tracheobronchitis the cultures yielded hemolytic streptococci or staphylococci in several instances. In the remaining cases, including all of those in which there were clinical and x-ray findings of pulmonary lesions resembling those of primary atypical pneumonia, the bacteriologic studies yielded no significant

pathogens. The role of the streptococci and staphylococci in relation to the tracheobronchitis is uncertain nor is the relation of the influenza virus to the tracheobronchial and the intrapulmonary lesions in these cases entirely clear. Such lesions are, of course, part of the pathologic picture of experimental influenza viral infection in animals[11] and have been observed, though rarely, in fatal human cases from which influenza virus was isolated but in which bacteria played no recognizable role.[12] On the other hand, the possibility that other microbial agents played a significant part but were not identifiable by the methods used cannot be entirely ruled out.

In view of the failure to demonstrate any definite action of aureomycin against experimental infections with influenza virus* it does not seem likely that the beneficial effects of this antibiotic, as reflected in the present cases by the rapid clinical improvement, was due to its action on the virus. This possibility is not necessarily excluded since in certain clinical infections aureomycin has proved more effective than was anticipated from the results reported in corresponding experimental infections in animals. It would seem more likely, however, that the bronchopulmonary lesions in the present cases were either due to or were aggravated by some agent other than the influenza virus. This agent could have been some bacteria similar to those isolated in a few of the cases but which were not identified in the others, or it may have been some other organism not usually considered pathogenic or not readily identified by the simple methods used. Moreover, the possibility cannot be excluded that some other non-bacterial agent which is susceptible to aureomycin was present either in symbiosis with the influenza virus, or as a secondary invader, or even as a normal inhabitant of the patient's respiratory tract that was activated by the influenza viral infection.

What has been said of the cases of influenza also applies to most of the cases of Group II. Three of these patients had simple nasopharyngitis and exudative tonsillitis that was probably due to the hemolytic streptococcus that was isolated from the cultures in each case, but adequate serologic studies to confirm this were not made.[10,14] The major illness in the other patients of this group could be classified as the common cold, or "clinical influenza" or "undifferentiated acute respiratory disease."[10] Some of these cases, especially those that were observed during the epidemic prevalence of influenza, may represent cases of this disease, but none of them could be identified as such by serologic tests or by the attempted virus isolations. In any event, the severity and duration of symptoms together with the apparently favorable response to aureomycin suggest that either the aureomycin was effective against the causative agent in these cases or, more likely, that some other aureomycin-susceptible agent was operative at the same time and was responsible for at least part of the clinical picture.

In the third group the five cases of "primary lobar pneumonia" most likely represent cases of pneumococcal, or possibly other bacterial pneumonia in which the bacteriologic methods were deficient. Failure to identify the causative organisms on several attempts in occasional cases of pneumonia that are later proved to be due to pneumococci or to other organisms are not unusual, even when antibacterial agents have not been used. In these five cases the results of aureomycin therapy were very similar to those observed in pneumococcal pneumonias and can best be explained on the assumption that pneumococci or some other common and susceptible bacterial pathogens were involved.

As to the remaining patients in Group III little need be said except to point out that partial or transient improvement followed the use of aureomycin in most of these cases. The results of any therapy directed against infections which occur as complications of other serious diseases are difficult enough to evaluate when the causative agents of those infections are readily identified. It is

* Only influenza B was mentioned in Wong and Cox's early studies.[13]

all the more difficult or well nigh impossible when the cause of the infection could not be determined and especially when the underlying disease is severe or intractable.

SUMMARY AND CONCLUSIONS

Aureomycin was used in the treatment of a miscellaneous group of forty-one cases of severe, acute respiratory infections with or without pneumonia.

In eighteen patients with proved influenza A infection, associated in most instances with bronchopulmonary involvement, the administration of aureomycin by mouth was followed by prompt defervescence and alleviation of symptoms, and the pulmonary lesions cleared rapidly. Pathogenic bacteria of possible significance were isolated from throat or sputum cultures only in a few of those patients in whom pulmonary lesions could not be demonstrated roentgenographically.

Similar rapid improvement occurred during aureomycin therapy in ten patients with severe, acute respiratory infections without pneumonia. Three of these patients had nasopharyngitis and exudative tonsillitis associated with beta hemolytic streptococci but no etiologic agent was identified in the others by the bacteriologic or serologic methods employed.

In five patients with classical signs and symptoms of lobar pneumonia but in whom bacteriologic studies failed to reveal the etiologic agent, aureomycin administration was likewise accompanied by a rapid termination of the acute disease.

Each of the remaining eight patients had pneumonia as a complication of other serious conditions and no microbial agent could be identified as the cause of the pneumonia. The results of aureomycin therapy in these cases were equivocal.

The significance of etiology in relation to the effectiveness of aureomycin was discussed in relation to the effects observed in these cases.

The bacteriologic studies in these cases were carried out with the assistance of Clare Wilcox and Janice M. Bryan and some of them were done in the Mallory Institute of Pathology by Marion E. Lamb and A. Kathleen Daly. All of the virus isolations and the serologic tests were done by Mildred W. Barnes, with the exception of the complement fixation tests for psittacosis and Q fever which were done either in the Department of Virus and Rickettsial Diseases of the Army Medical Center through the courtesy of Dr. Joseph E. Smadel or in the Section of Viral and Rickettsial Research of the Lederle Laboratories through the kindness of Dr. Herald R. Cox.

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Aureomycin in the Treatment of Anthrax*

HERMAN GOLD, M.D.
Chester, Pennsylvania

AUREOMYCIN produced from a strain of Streptomyces by Dr. B. M. Duggar and associates has been the subject of intense clinical research.[1–9] We wish to add anthrax to the list of infections susceptible to treatment with aureomycin, hence this brief preliminary report.

CASE REPORTS

CASE 1. Mr. E. W., a white male fifty-two years of age weighing 167½ pounds, was seen by us on January 13, 1949, because of a small itchy "pimple" on the dorsal surface of the left wrist. It was first noted two days previously. Examination revealed a very small red papule with no surrounding edema. There was no adenopathy or fever. Because of the patient's occupation as a carder in a mill which had been the source of many cases of anthrax, this diagnosis was entertained but a smear revealed only red blood cells. On the 14th the papule was flatter; the only complaint was intense local itching. On the 15th the papule appeared to be absorbing. The patient continued to work but on the night of the 17th his wrist began to swell and was painful on motion. There was itching and a burning sensation at the site of the lesion which when seen on the 18th was the size of a nickel. A ring of fine vesicles surrounded the edge of the blue-red papule. Edema of the dorsum of the hand and wrist with bright erythema of the skin was present. A small slightly tender lymph node was palpable in the left axilla. The temperature was normal. Clinically there was no question concerning the diagnosis of anthrax. This was confirmed by recovery of Bacillus anthracis on smear and culture. *In vitro* antibiotic sensitivity tests were run on this culture at the Antibiotic Research Department, Children's Hospital of Philadelphia with the following results: (1) Aureomycin, very sensitive, growth inhibited by 0.25 μGm./cc.; (2) streptomycin, moderately sensitive, growth inhibited by 3 μGm./cc.; (3) penicillin, resistant, growth inhibited by 30 units/cc.

The patient was treated in ambulatory fashion with aureomycin (duomycin), 750 mg. by mouth every four hours. One hour after the second dose (five hours after institution of therapy) a second smear and culture from the lesion was made without any change being noted.

The next morning the patient reported to the office feeling well except for slight itching at the site of the lesion. However, the edema had increased considerably, extending dorsally from the metacarpal joints to the upper one-third of the forearm. The skin was bright red and tender at the margin of the spreading edema. The lesion showed large bluish vesicles that oozed freely. Axillary adenopathy was unchanged. The temperature was 99 to 99.4°F. Smear and culture, taken twenty-three hours after aureomycin therapy was started, were still positive for anthrax. On the 20th, forty-eight hours after antibiotic treatment was begun, the edema of the forearm had cleared and the dorsum of the hand was only slightly swollen and dusky red in color. The lesion had the characteristic appearance of an anthrax "pustule." Smear from the lesion showed a definite decrease in the number of bacilli with unmistakable signs of degeneration but the culture was still positive. On the twenty-first the lesion showed a central dry black eschar, 5 mm. wide with slight induration around it. The hand was normal except for some discoloration of the skin. There was no adenopathy. The last dose of 750 mg. of aureomycin was taken at 9 A.M., thereafter 500 mg. were ingested every four hours for three doses, when the interval was lengthened to six hours. On the 22nd the patient felt fine except for some looseness of the bowels. The lesion was dry, flat and black. There was no edema or adenopathy. Smears and cultures were negative for anthrax bacilli. On the 24th the eschar began to separate at one margin; otherwise, there was no

* From The Chester Hospital, Chester, Pa.

change. Medication was stopped after total consumption of 19.75 Gm. of aureomycin in six days. The blood count, urinalysis and sedimentation rate were normal.

The eschar had completely separated on the 31st when the patient returned to work. The period of disability was fourteen days. The small, shallow, granulating ulcer healed in three weeks.

CASE II. Mrs. A. F., a white female twenty-seven years of age weighing 95 pounds, was well until April 8, 1949, when she noted a small pimple on the right hand just above the thumb. She was a spinner in the mill where the first patient worked. The next day pain and tenderness developed in the right axilla, especially after motion, which prompted her to seek medical advice. Examination revealed a very small papule on the right hand without swelling or redness. The epitrochlear nodes were not palpable but a tender lymph node the size of a marble was outlined in the right axilla. The temperature was 98.6°F. Dr. G. Sickel of Chester Hospital demonstrated anthrax bacilli on smear and culture of the lesion. Sensitivity tests on this culture were identical to those in Case I except that the organism was inhibited by 5 units of penicillin.

April 10, 1949, the pustule was the size of a split pea with an area of redness and edema around it the size of a twenty-five-cent piece. There was local itching and burning. Two large tender lymph nodes were palpable in the axilla. The temperature was 99.2°F. Aureomycin,* 750 mg. every four hours, was ordered. On April 11, 1949, the lesion was flat, black and dry but the dorsum of the hand was moderately swollen and bright red in color but not painful. One single node was outlined in the axilla which did not appear to be as painful. Marked nausea and occasional vomiting developed. Aureomycin dosage was reduced to 500 mg. every four hours. Smear of the lesion showed an occasional anthrax organism but the culture was positive. On April 12, 1949, there was increased edema of the hand but the erythema of the skin had lessened. The pustule was dry and the size of a dime. The axillary node was barely palpable. The temperature reached 100°F. and the blood count and urinalysis were normal. Intense nausea and repeated vomiting were very distressing.

On April 13, 1949, the hand was only slightly swollen and the skin was faintly red. The papule was flat and dry; the axilla was normal. Aureomycin was not tolerated even when given as one capsule (250 mg.) every six hours. Medication was stopped after 11.25 Gm. were ingested (some was lost through vomiting). April 15, 1949, the patient was symptom-free and her hand was normal in contour. The eschar began to separate on the 18th and came off a week later. The patient returned to work on April 25, 1949. The ulcer gradually filled with clean granulation tissue and healed in two weeks.

* Supplied by Lederle Laboratories, Pearl River, N. Y.

COMMENTS

Case I involved a rather unusual form of cutaneous anthrax in that the classical manifestations of the local lesion did not fully develop for seven days after the appearance of a papule. However, treatment with aureomycin was not started until edema was manifest in both cases. Clinical control was achieved in forty-eight to seventy-two hours but bacteriologic cure was not established until the fourth to fifth day of treatment. Clinically these patients responded as rapidly or perhaps a little faster than patients previously treated by us with large doses of penicillin.[10] Bacteriologically the response judged by the failure to recover anthrax bacilli from the lesion was slower in these subjects than in penicillin-treated patients.[11–13] However, this finding is subject to many variables. In this regard our previous experiences with serum and sulfonamides in the treatment of anthrax[14] taught us that clinical control of the infection as judged by disappearance of the edema, erythema, pain and toxicity often occurs before bacteriologic control is achieved.

Exacerbation of the disease process as evidenced by increasing edema and painful tender erythema of the skin was noted for twenty-four to forty-eight hours after institution of treatment; thereafter, these local signs as well as regional adenopathy subsided promptly. This was also noted following penicillin therapy.[13] Like other therapeutic agents[12–14] aureomycin did not seem to affect the course of development of the anthrax pustule. The question of optimum

dosage and length of treatment requires further study.

The advantages of oral medication, ease of administration, lack of sensitizing reactions and benefits to be derived from the fact that this therapy allows for ambulatory management need no further elaboration. Moreover deaths from anthrax do occur even after the use of large doses of penicillin[15] hence the advent of another potent antibiotic for the treatment of anthrax is to be welcomed.

Antibiotic sensitivity tests were performed through the kindness of Dr. C. M. Whitlock and Mrs. S. Tashman, Philadelphia, Pa.

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Acute Serofibrinous Pericarditis of Undetermined Cause*

A Study of Twenty-seven Cases

ROBERT L. LEVY, M.D. *and* MYRON C. PATTERSON, M.D.
New York, New York

THERE is a group of patients with acute pericarditis who present a distinct clinical picture although the severity and duration of the illness may vary. Usually a history is obtained of an antecedent respiratory infection. There is no other evidence of cardiovascular disease. Pain in the chest is the dominant symptom at onset. The exudate is serofibrinous, never purulent. Recovery is the rule, and the cause is not known.

Mention of pericarditis of obscure etiology is made in a few of the classic monographs on diseases of the heart published during the later years of the nineteenth century; in the modern texts it is referred to briefly or not at all. The first report which we have found in which an infection of the upper respiratory tract apparently was related to non-suppurative pericardial involvement was that of Comer[1] who in 1927 recorded an instance of pericarditis with effusion following acute sinusitis in a man thirty-five years of age. Ten days after the evacuation of foul-smelling pus from the left antrum the patient was well. Cultures were not taken. However, it was Barnes and Burchell[2] in 1942 who focused attention on this type of pericarditis and stressed the importance of distinguishing it from that which follows acute myocardial infarction. Since then reports of additional cases have appeared and have amplified their description.[3] A number were observed in the Armed Forces in World War II, some of them in association with primary atypical pneumonia. In a few pleural effusions also were noted. A summary of the main points of interest was made in 1947 by Burchell.[4]

Although this is not a common disease, neither is it rare. Of 292 instances of acute pericarditis observed at the Presbyterian Hospital during the past fifteen years twenty-two (7.5 per cent) were placed in this diagnostic category. In addition to these twenty-two cases five others seen in outside consultation practice have been included in the analysis which forms the basis of this study. The cases were carefully chosen and all were rejected in which any possible known etiologic factor, such as coronary occlusion, rheumatic fever, uremia, tuberculosis or pyogenic infection within the pericardial sac, may have played a role. None of the patients died; this fact, in a sense, confirms the correctness of the diagnosis while precluding the opportunity of final proof.

Because the syndrome may simulate others having a more serious prognosis, a clear definition of the clinical features is of first importance. Follow-up observations bearing on the subsequent course have also been made, with particular reference to the possible later development of constrictive pericarditis.

CLINICAL FEATURES

Of the twenty-seven patients twenty were males and seven were females. They ranged

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital. This study received support from the John D. and Kathryn R. Burger Fellowship Fund of the New York Heart Association. Read before the Section on Medicine, New York Academy of Medicine, March 15, 1949.

in age from twelve to fifty-three years, with an average of thirty-five years. Twenty-two were white and five were negroes. In no case was there a history of previous rheumatic fever or chorea. In three instances the patients stated that they had had scarlet fever but this had preceded the onset of pericarditis by many years. Eight patients were subject to frequent infections of the upper respiratory tract.

TABLE I
SYMPTOMS IN TWENTY-SEVEN CASES

Antecedent respiratory infection	23
Onset—Acute	17
Gradual	10
Precordial or substernal pain	26
Severe	19
Moderate	7
With radiation	14
Intermittent	17
Continuous	9
Intensified by deep breathing, body movement or cough	21
Dyspnea or orthopnea	14
Nausea and vomiting	1

Initial Diagnosis. The initial diagnosis was acute pericarditis of unknown cause in eight, acute cardiac infarction in six, acute serofibrinous pleurisy in four and acute rheumatic heart disease with pericardial involvement in three. Other diagnoses made included bronchopneumonia, lobar pneumonia, tuberculous pericarditis, cardiac hypertrophy of unknown etiology and fever of obscure origin.

Symptoms. An infection of the respiratory tract preceded the onset of pericarditis in twenty-three patients. In fifteen this was described as a cold; there were three instances of bronchitis, two of pneumonia of undetermined etiology (probably due to a virus), one of primary atypical pneumonia, one of pharyngitis and one of acute purulent maxillary sinusitis. These infections antedated the pericardial involvement by intervals ranging from a few days to four weeks, with an average of ten days. (Table I.)

The onset was acute in seventeen; gradual in ten. By an acute onset is meant sudden appearance of sharp pain in the chest. In the cases with gradual onset the discomfort in the chest was less intense and tended to increase over a period of several days. Pain was present in all but one patient and lasted from a few minutes to ten weeks; the average duration was three weeks. The pain was precordial or substernal and was usually severe. In fourteen cases it radiated to the left shoulder, left arm, back or abdomen and in one patient was felt in the fourth and fifth fingers of the left hand. It was more often intermittent than continuous and in twenty-one cases was aggravated by deep breathing, cough or movement of the body. Difficulty in breathing was experienced by fourteen patients and in five of these was sufficiently marked to require the erect posture for comfort. One patient was nauseated and vomited.

TABLE II
SIGNS IN TWENTY-SEVEN CASES

Fever at onset (initial temperature known in 21)	19
Friction rub	19
Heard on first day of illness	9
Heard when first seen (not on first day of illness)	10
Tachycardia (rate over 80 per min.)	18
Fall in systolic pressure greater than 20 mm. Hg	7
Gallop rhythm	1
Leukocytosis (counts made in 23)	20
Increased sedimentation rate (taken in 25)	24
Electrocardiographic changes	26
RS-T elevation	19
T-wave inversion	19
Lowering of T-waves without inversion	4
Cardiac arrhythmia	3
X-rays of chest taken	25
Cardiac enlargement	20
Pneumonitis	7
Pleural effusion	14
Left only	8
Bilateral	6

Signs. The temperature at onset was known in twenty-one patients, of whom nineteen had fever on the first day of illness. (Table II.) Of the two who were afebrile in the beginning one developed fever on the third day and the other never showed an elevation of temperature. This patient was a negro with severe chest pain, loud friction rub, striking RS-T elevations in the electrocardiogram, leukocytosis and no evidence of tuberculosis or rheumatic fever. He was in the hospital for two and one-half weeks, was discharged well and, when seen two years later, had no symptoms or signs of cardiovascular or pulmonary disease.

The range of highest temperature was from 100.4° to 105°F; the average high level was 102.7°F. The duration of fever was from one day to two months, with an average of four weeks.

A pericardial friction rub was heard in nineteen patients. However, of the eight in whom no rub was noted five were not seen until at least two days after the onset. In half of the cases in which a rub was present it was heard on the first day of illness; in six others not examined at the onset it was heard on the first day on which the patient was seen. The rub persisted for a period ranging from one day to four weeks, with an average duration of nine days.

Tachycardia, with heart rate over 80 beats per minute, was observed in eighteen patients. The maximal rates ranged from 104 to 140, with an average of 123 beats per minute. Acceleration of rate lasted from three days to nine weeks, with an average of three weeks. In only one instance was a gallop rhythm heard. A fall in systolic blood pressure greater than 20 mm. Hg was recorded in seven cases.

It is noteworthy that in not a single instance were there signs of shock or of cardiac insufficiency.

Leukocytosis (over 10,000 per cu. mm.) occurred in twenty of the twenty-three patients in whom counts were taken. The peak counts in the cases with leukocytosis ranged from 10,600 upward, with an average of 20,400 per cu. mm. The highest count was 55,000 which was obtained in a patient in whom the pericarditis was associated with primary atypical pneumonia. The percentage of neutrophiles rose as high as 97 in the case with the highest leukocytosis, although in only four instances was the percentage above 89. In ten cases the polymorphonuclears, in the presence of leukocytosis, were under 80 per cent. Leukocytosis was present from one day to eight weeks; the average duration was three weeks.

The sedimentation rate of the red blood corpuscles was increased (over 20 mm. in one hour, Westergren method) in twenty-four of twenty-five patients in whom determinations were made. The increase was noted on the first day on which the patient was seen in seven instances and within four days thereafter in the remainder. The highest value was 125 mm. in one hour; the average peak was 81 mm. The duration of the increase ranged from ten days to fourteen weeks. In one of the cases in which the rise lasted for fourteen weeks there was an associated primary atypical pneumonia; in this patient the peak of leukocytosis was 55,000, as previously noted. In the other case with similarly prolonged elevation, bilateral pleural effusion was present. In the one patient without increase in sedimentation rate the entire duration of illness was two weeks although fever, leukocytosis, friction rub, electrocardiographic changes and cardiac enlargement were all observed.

Electrocardiograms. The three standard limb leads and lead 4F were taken routinely. Additional chest leads occasionally were recorded. Electrocardiographic changes were present in all but one patient. This was a young man with severe pain in the chest, fever, leukocytosis, elevated sedimentation rate and pericardial friction rub. Elevation of the RS-T segments was observed in every case in which records were taken during the first few days of illness (nineteen of twenty-six) with the one exception just noted. It was an early change. Such elevation was generally present in all four leads, but occasionally in Leads I and II only, Leads II and III only, or in Leads I and II combined with III or IV. Inversion of the T-waves occurred in nineteen cases, lowering without inversion in four, and in three there was neither inversion nor lowering. T-wave inversion occurred later than RS-T elevation. Transitory arrhythmia occurred in only three instances. In one, this consisted of premature auricular contractions and a shifting pacemaker; in two, premature ventricular contractions were present. The changes in the form of the electrocardiogram persisted from two weeks to three months, with an average of six weeks. It is significant that prolongation of the P-R interval, so often

seen in acute rheumatic fever, was not observed in any patient.

X-rays. Of twenty-five cases in which adequate x-ray studies were made twenty showed cardiac enlargement. In five this was regarded by the roentgenologist as due to pericardial effusion and in sixteen to cardiac dilatation (in one both effusion and dilatation were considered to be present). We have sometimes found it difficult to distinguish between the enlargement due to dilatation and that which results from a small effusion. Evidence of enlargement, by x-ray examination, lasted from two to ten weeks, with an average of five weeks.

Involvement of the lungs was observed in the x-ray films in seven patients. In two this was in the form of peribronchitis of undetermined etiology, in four bronchopneumonia of unknown cause was observed and in one instance the picture was that of primary atypical pneumonia. Pleural effusions were present in fourteen cases; in eight the fluid was in the left pleural cavity only whereas in six it was bilateral. No effusion occurred on the right side alone.

Bacteriologic Studies. Thirty-eight blood cultures were taken in thirteen cases; all were negative. The usual media and aerobic technic ordinarily were employed; in a few instances anaerobic cultures also were made. From 10 to 100 cc. of clear, straw-colored fluid was aspirated from the pericardium in three cases; cultures showed no growth. Centrifuged material from one case was inoculated into a guinea pig; no tuberculous lesions developed.

Aspiration of pleural fluid was done sixteen times in nine patients. From a few hundred to 1,100 cc. were removed at one tap. The fluid was straw-colored except on one occasion when blood was present, presumably due to trauma. Cultures were made on each occasion and guinea pig inoculation was done five times. The results were uniformly negative.

The pleural fluid obtained by aspiration was examined microscopically in four cases. The specific gravity ranged from 1.015 to 1.022. The leukocyte count was not more than 2,000, with monocytes predominating except in one instance. This was a case of pneumonia of undetermined etiology in which the polymorphonuclears in the fluid comprised 90 per cent of the total; during convalescence this percentage fell to 36. Similar examinations of the pericardial fluid were not done.

Throat cultures were obtained seventeen times in fourteen patients. In four instances organisms were grown which might possibly have been of significance. A hemolytic streptococcus was obtained in two cases and pneumococcus type XII and non-hemolytic staphylococcus aureus in one case each. In the one patient with purulent maxillary sinusitis, hemolytic staphylococcus aureus was grown from the washings. It seems highly unlikely that the pericardium was infected with any of these bacteria.

Determination of the antistreptolysin titer was done twenty-five times in sixteen patients. In twenty-two instances the value was below 200 units; in one case it reached 500 units and in two cases it rose to 1,250 units. In two of the patients with a high titer hemolytic streptococcus was grown in the throat culture. In no instance, however, was there clinical evidence of rheumatic fever either during the acute illness or in the follow-up examination.

Antibiotic and Drug Therapy. Penicillin alone was given to six patients; in five it was injected intramuscularly and in one both by this route and intrapleurally. In one patient who was severely ill penicillin and streptomycin were given intramuscularly, intrapleurally and intrapericardially. Sulfadiazine was given by mouth to one patient. No apparent benefit resulted from any of these forms of therapy and the nineteen patients who were treated without specific measures apparently fared equally well.

Duration of Illness. This ranged from two weeks to three months; the average was seven and one-half weeks. All of the patients recovered.

Recurrences. There were four recurrences of pericarditis in three patients. In two these appeared eight and ten years, re-

spectively, after the initial attack. One patient had two recurrences, five weeks and three months after the first episode. All of the recurrent attacks were relatively mild and lasted, on the average, about three weeks. In only one instance did an upper respiratory tract infection antedate the onset of the recurrence. In this case acute maxillary sinusitis preceded both the initial and recurrent attacks. Although a friction rub was present in each recurrence, pericardial effusion could not be demonstrated in any; but in one case bilateral pleural effusion was present. Characteristic electrocardiographic changes were observed in each recurrent attack. All of the patients recovered completely.

FOLLOW-UP OBSERVATIONS

Twenty-three of the patients were reexamined at intervals ranging from six months to sixteen years following their acute illness; this interval was more than two years in seventeen instances. The average duration of the follow-up period was five and one-half years. At the final follow-up visit a detailed history was taken, a complete physical examination was made and an electrocardiogram and 2-meter film of the chest were taken. In most of the cases fluoroscopic examination of the heart supplemented the x-ray film.

The general health since the attack of pericarditis was good except in two patients. One of these developed a peptic ulcer four years after the attack of pericarditis; the other suffered from mild, acute serofibrinous pleurisy six months after the pericardial episode. In no instance were there symptoms or signs of congestive heart failure. Two patients complained of mild, sticking precordial pains, unrelated to effort.

In one patient a soft, apical systolic murmur, persisting in all phases of forced breathing and in the erect position, was heard both during the acute illness and at the follow-up examination. There was no evidence of rheumatic fever in this woman, who was fifty-three years old when first seen. The patient's physician stated that the murmur had been present for a number of years prior to the attack of pericarditis.

In the x-ray films the size and contour of the heart and aorta were within normal limits in every case. Fluoroscopy was done in seventeen cases; in two the roentgenologist thought that pleuropericardial adhesions could be demonstrated in the region of the cardiac apex. There were no changes suggesting constrictive pericarditis.

The follow-up electrocardiograms were within the normal range in every instance.

ILLUSTRATIVE CASES

The following three case summaries serve to illustrate various types of this disease:

CASE I. F. A., a white male, aged forty-seven years, was a surgeon who never had been seriously ill. Early in April, 1934, he had an ordinary head cold. One week after the onset, on April 8th, while walking he had a sudden precordial pain which was aggravated by taking a deep breath. He went home and called his family physician who heard a friction rub and raised the question of coronary occlusion with myocardial infarction. On the next day it seemed quite clear that the condition was due to acute pericarditis following infection in the upper respiratory tract. The temperature by rectum was 100.8°F. on the first day; the leukocyte count was 10,000 per cu. mm. There was no fever thereafter. He remained in bed for eleven days. The friction rub disappeared in the course of three days. He returned to work at the end of fifteen days without taking a holiday for further convalescence.

The electrocardiogram on April 9th showed slight elevation of the RS-T segments in the 3 limb leads. (Fig. 1.) In a record taken on April 11th this was less marked and on May 18th the record was normal.

The patient was seen at irregular intervals during the next fourteen years. He continued to work actively as a surgeon. Cardiovascular examinations were negative. The blood pressure ranged from 114 to 120 mm. Hg systolic; 70 to 80 diastolic. In the winter he took no exercise but in the summer he swam and played golf.

The last follow-up examination was made exactly fourteen years after the initial attack. He was sixty-one years of age and was still working hard. He seldom played golf but swam

in the summer. There had been no recurrence of the pericarditis and he had not suffered from any serious illness during the fourteen-year period. He rarely had a cold.

The heart was not enlarged either on percussion or by x-ray examination. The rhythm was regular; the rate was 64. The sounds were of normal intensity and clear. The blood pressure was 124/76. Fluoroscopic examination showed no adhesions between the pericardium and the diaphragm. The electrocardiogram was normal. (Fig. 1.)

Although this patient never was gravely ill the onset was sufficiently acute and painful to suggest the diagnosis of cardiac infarction. The ability to return to work at the end of two weeks and the absence of marked electrocardiographic changes indicated minimal myocardial involvement.

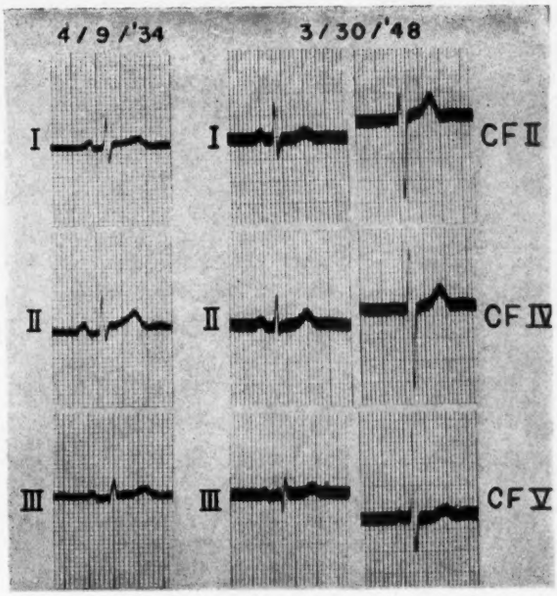

FIG. 1. On April 9, 1934, the day following the acute onset of pain, the electrocardiogram shows slight elevation of RS-T segments in the three standard limb leads. On March 30, 1948, fourteen years later, the record is normal; three precordial leads are also pictured. Case I.

CASE II. F. P. R., a white male, aged thirty-six years, was a business executive. He had enjoyed unusually good health and rarely suffered from a cold or sore throat. Tonsillectomy had been performed in youth. He played squash twice a week in the winter and golf in the summer. There had been no symptoms referable to the heart.

The present illness began nine days before admission to the hospital, with a sore throat and fever which lasted three days. On the day before admission he was awakened in the early morning hours by severe substernal pain. His physician stated that he was not in shock. The pharynx was slightly injected and a loud pericardial friction rub was heard over the entire precordial area. A diagnosis was made of coronary occlusion with cardiac infarction.

The initial examination showed a temperature by rectum of 101°F., a slightly enlarged heart, somewhat distant heart sounds and a loud pericardial friction rub. He did not appear to be very ill. The throat was still red but no exudate was seen. The leukocytes numbered 19,000 with 81 per cent polymorphonuclears. The erythrocyte sedimentation rate was 32 mm. in one hour. The electrocardiogram (Fig. 2) showed elevation of the RS-T segments in all of the four leads taken. X-ray of the chest showed slight enlargement of the heart shadow. The diagnosis was changed to acute, serofibrinous pericarditis of unknown cause.

For four days low-grade fever persisted, the highest level reached being 100.4°F., and he continued to complain of substernal pain radiating to the left shoulder. The pericardial rub was not heard after the second day in the hospital. He received penicillin by injection for four days but it is doubtful whether it exerted any beneficial action. The lungs remained clear. On the seventh day of illness the heart sounds became fainter and frequent premature beats were noted. The venous pressure at this time was 125 mm. of water. It was not considered necessary to tap the pericardial sac.

After the first six days the course was uneventful. During the third week the leukocyte count returned to normal. The sedimentation rate, after reaching a peak of 42 mm. on the fourth day, tapered off to 10 mm. at the end of the sixth week. A determination of the antistreptolysin titer on the tenth day was 1,250 units, which merely indicated that he had had a streptococcal infection. Certainly the clinical picture was not that of rheumatic fever.

A series of electrocardiograms (Fig. 2) showed changes characteristic of acute pericarditis. These persisted, though gradually diminishing in degree, for two months. A 2-meter x-ray film of the chest at the end of five weeks showed the cardiac silhouette to be normal in size and shape.

The patient was discharged at the end of six weeks. He remained quietly at home for a month

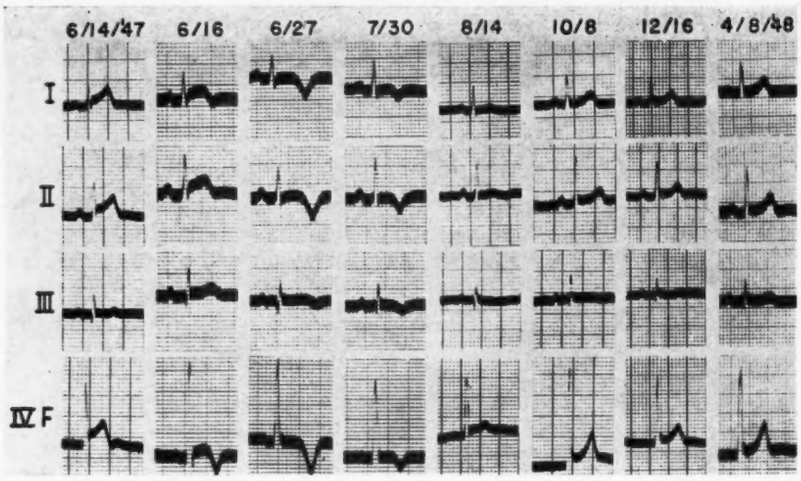

FIG. 2. A series of electrocardiograms showing, in the first record taken on the day after the acute onset of pain, elevation of RS-T segments. Later there is inversion of T waves and, subsequently, return toward normal. The final record taken nine months after the beginning of illness still shows slight elevation of RS-T segments. Case II.

and resumed work four months after the onset of his illness. He was seen at intervals by his physician and an electrocardiogram was taken once a month. The final follow-up examination was made eleven months after the onset of the acute illness. There was no pain in the chest. He still felt "flabby" and thought he required more sleep than formerly. The heart sounds were of normal intensity and clear. The blood pressure was 146/90. An x-ray film of the chest showed no cardiac enlargement. The electrocardiogram (Fig. 2, April 8, 1948) still showed slight elevation of the RS-T segments in Leads II, III and 4F but normal T waves throughout.

Pericarditis in this case followed nine days after a sore throat, presumably streptococcal in origin. The clinical picture and course did not suggest rheumatic fever. There were no signs of valvulitis at any time. The electrocardiographic changes were marked and persistent, indicating significant involvement of the superficial layers of the myocardium, with subsequent healing. Enlargement of the heart was due more to dilatation than pericardial effusion, although it seems probable in view of the slight elevation in venous pressure that a small amount of excess fluid was present. This may be regarded as an instance of the moderate form of the disease, without pleural or pulmonary involvement.

CASE III. W. T., a white male, aged thirty years, was a research chemist. His general health had been good and he was not subject to respiratory infections. His acute illness began one week before admission to the hospital with symptoms suggesting to his local physician the diagnosis of influenza. Four days after onset he felt pain beneath the sternum, aggravated by deep breathing and radiating to the left shoulder. His temperature, which during the first few days was not over 100.5°F., rose to 103°F. He was given 30 gm. of sulfadiazine without apparent benefit.

When first seen in the hospital he was slightly dyspneic and cyanotic. The temperature was 102.4°F. The heart was enlarged on percussion, the rate was 90, the rhythm was regular and a loud pericardial friction rub was heard. The blood pressure was 108/90. There was dullness over both lower lobes of the lungs.

A film of the chest taken at the bedside with a portable machine (Fig. 3) showed pleural effusion at both bases and enlargement of the heart suggesting pericardial effusion. There was no intrapulmonary disturbance. The leukocyte count was 15,000 with 72 per cent polymorphonuclears. The Kline test of the blood was negative. The urine gave a two-plus test for albumin and microscopically showed a few leukocytes. The sedimentation rate of the erythrocytes was 71 mm. in one hour. The electrocardiogram showed slight elevation of the RS-T segments in Leads I and II.

Two days after admission the venous pressure

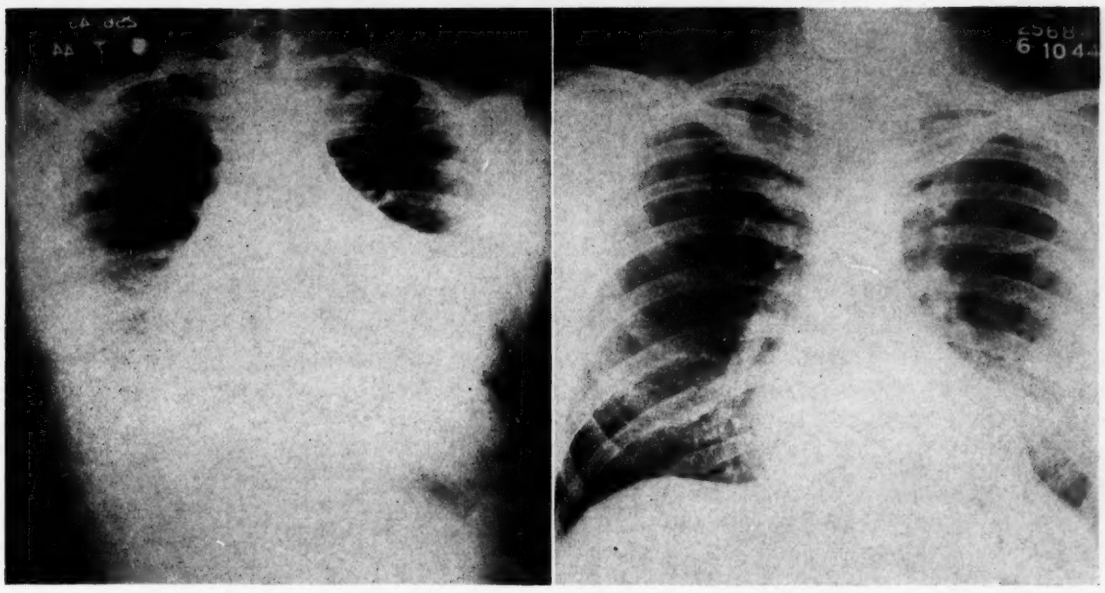

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FIG. 3. X-ray of the chest taken at the bedside four days after the appearance of pain. There is marked cardiac enlargement and fluid is present in both pleural cavities. Case III.
FIG. 4. X-ray of the chest taken one month after the picture shown in Figure 3. The heart shadow is much smaller. There is slight thickening of the pleura at the left base but there is no evidence of intrapulmonary disease. Case III.

was read at 148 mm. water and a pericardial tap was done. This was unsuccessful on the first attempt but when the needle was again inserted 120 cc. of blood-tinged fluid was removed. The blood was believed to have been the result of trauma resulting from the first puncture.

The patient was tachypneic and apprehensive and was placed in an oxygen tent. Fever persisted for seventeen days, with a peak of 104.4°F. on the fourth hospital day. The heart rate ranged from 80 to 120 beats per minute. He was extremely ill and uncomfortable. Thoracentesis was performed first on the right with removal of 1,000 cc. of clear, amber-colored fluid, and later on the left with removal of 1,100 cc. of similar fluid. Following the second chest tap the temperature fell to normal in four days and there was no recurrence of fever. He was discharged at the end of the ninth week in the hospital.

The course in this case was stormy. The highest temperature was 105.4°F.; the highest heart rate was 132 per minute. The venous pressure remained elevated for ten days, fell to normal and rose again to 128 just before the second thoracentesis. The arterial blood pressure remained within normal limits—from 104 to 142 systolic; 66 to 72 diastolic. The leukocyte count during the acute stages ranged from 14,000 to 26,850 per cu. mm. with polymorphonuclears from 75 to 81 per cent. It was still 11,750 shortly before discharge. At its peak the erythrocyte sedimentation rate was 71 mm., which was the figure observed on the day of admission. It returned to a normal level at the end of the sixth week.

Four blood cultures yielded no growth. The fluid removed from the pericardium was contaminated by blood. The fluid from the pleural cavities showed a specific gravity of 1.022. It contained 5,100 leukocytes and 11,000 red blood cells (probably due to trauma). A differential count of the leukocytes showed a predominance of polymorphonuclears. Cultures of all of these fluids showed no growth, both aerobically and anaerobically. Some of the pericardial fluid was inoculated into a guinea pig with negative result with respect to tuberculosis. The antistreptolysin titer on one determination was 55 units. Agglutination tests for typhoid, paratyphoid, typhus, brucellosis and tularemia were negative.

X-ray examinations of the chest (Figs. 3, 4 and 5) showed gradual return of the heart to normal size and complete clearing of both lung fields. At no time were shadows observed indicating intrapulmonary disease.

Electrocardiograms (Fig. 6) showed serial changes characteristic of pericarditis, with early elevation of the RS-T segments in Leads I, II and 4F, and later inversion of the T waves in all

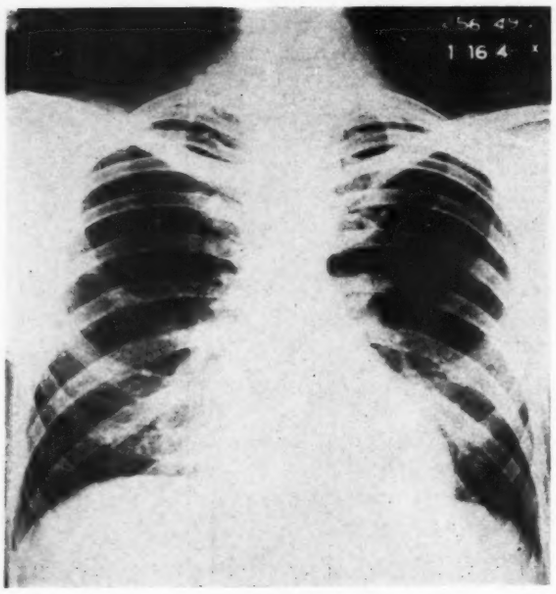

FIG. 5. X-ray of the chest taken three and one-half years after the acute illness. The heart is normal in size and shape; the lungs are clear. Case III.

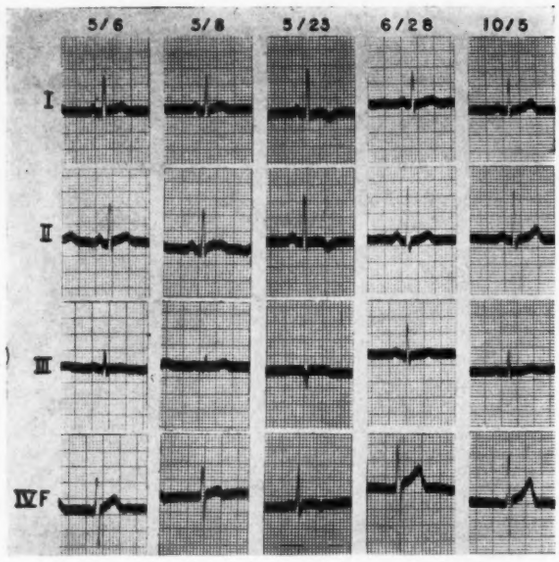

FIG. 6. A series of electrocardiograms showing early elevation of RS-T segments, later inversion of T waves and subsequent return to a normal pattern. Case III.

leads. The form of the complexes returned to normal by the end of the eighth week.

Therapy included the use of sulfadiazine at the onset, salicylate during the early days in the hospital and subsequently the parenteral administration of penicillin in doses of 200,000 units daily for ten days. In addition, 40,000 units were injected into the left pleural cavity at the time of the thoracentesis. There was no evidence that any of these drugs exerted a favorable influence on the course of the disease.

Pleurisy with effusion recurred on the left side one month after leaving the hospital. The patient was cared for in Boston by Dr. Chester Keefer from whom notes of his illness were obtained. Aspiration was not necessary and fever lasted only five days.

Final follow-up examination was made three and one-half years after the initial acute illness. He had been perfectly well and was free from cardiac symptoms. The heart sounds were of normal intensity and clear. The blood pressure was 126/80. The electrocardiogram was normal. A 2-meter film of the chest showed no cardiac enlargement and no evidence of pleural or pulmonary disease.

This patient was gravely ill and extremely uncomfortable yet at no time were there signs of cardiac insufficiency. His illness followed an acute upper respiratory infection of the type commonly regarded as due to a virus. No etiologic agent was determined, although many were excluded as possible contributing factors.

COMMENT

The variability of the clinical picture and associations of this type of pericarditis favors the concept that the etiology likewise may be diverse. In those instances which occur after a common cold or in the course of primary atypical pneumonia it is reasonable to ascribe pericardial as well as pleural involvement to infection with a virus. The majority of cases fall into this category. Extension through lymphatic channels from the upper respiratory passages or directly from the lungs is a likely mode of spread. When there is preceding bacterial infection of the nasopharynx or sinuses, some other mechanism must be sought to explain the sterility of the pericardial exudate. It is quite possible that in such cases the reaction in the pericardium is of an allergic nature. Support for this idea is found in two of our cases, in one of which pericarditis appeared nine days after a sore throat, presumably streptococcal in origin, and in the other one week after infection in an antrum due to a hemolytic staphylococcus aureus. In the second case a relapse occurred ten years

later, this time two weeks after purulent exudate, containing a similar organism, was obtained from the same antrum. The duration of the latent period between initial infection and pericardial involvement is comparable to that usually required for the development of an immune response. It is noteworthy, also, that all of the recurrences in our series were milder than the original attacks and recovery was quicker, suggesting that possibly local desensitization had taken place. Finally, three cases may be cited[5] in which pericarditis followed the injection of diphtheria or tetanus antitoxin. In one pleural effusion also appeared. Severe serum disease was present in all of these patients and exudation into the pericardium was regarded as part of the general reaction.

The proper diagnosis is arrived at largely by exclusion of known etiologic factors. Usually it is not difficult to rule out the presence of tuberculosis or rheumatic fever. The importance of a history of an infection of the upper respiratory tract within the past two or three weeks or the presence of primary atypical pneumonia have already been stressed. Pericarditis following acute myocardial infarction is the most frequent source of confusion. Helpful points of difference are the occurrence, in the type under discussion, of fever and an elevated sedimentation rate on the first day of illness, as well as the presence of a friction rub at the onset of discomfort. Changes in the form of the electrocardiogram likewise are distinctive.[2] In brief, in pericarditis not associated with cardiac infarction the diagnostic pattern consists of elevation of the RS-T segments with upright dome-shaped or peaked T waves early in the disease and negativity of the T waves later in its course. There is no depression of the RS-T segments at any time and no Q pattern develops in the standard limb or precordial leads. It is also noteworthy that in none of our cases was there prolongation either of the P-R or Q-R-S interval. The changes observed are believed to be due to epicardial involvement yet the function of the heart muscle is never depressed sufficiently to induce congestive failure. Complete regression of these changes indicates that the injury to the myocardium is not severe, so that healing occurs without the formation of damaging scars.

Enlargement of the heart, as determined at the bedside and by x-ray examination, appears to be due more often and to a greater extent to dilatation than to pericardial effusion. Successful aspiration of the pericardial sac yields only small amounts of fluid; and the contour of the cardiac silhouette in the roentgenogram differs, as a rule, from that caused by the large effusions observed in the rheumatic and tuberculous varieties. The mechanism of the cardiac dilatation is not clear; the most plausible explanation assumes the presence of a toxic myocarditis which results in a loss of tone and lengthening of the muscle fibers but not to an extent sufficient to impair the capacity of the heart as a pumping mechanism. Within these limits dilatation may be regarded as compensatory and physiologic. It seems remarkable that with such striking degrees of cardiac enlargement congestive failure and significant arrhythmias are not encountered. A comparable though less marked increase in the size of the heart has been demonstrated in the course of acute lobar and lobular pneumonia.[6]

At the present time no effective specific form of therapy is available. Penicillin may be given when a bacterial infection is present in the upper respiratory tract but its use, as well as that of streptomycin and sulfadiazine, has not exerted a demonstrable beneficial action on the pericardial or pleural lesions. Because of its antiviral action and the favorable results recently obtained with aureomycin in the treatment of primary atypical pneumonia,[7] this newer antibiotic merits trial.

The immediate prognosis, even in patients apparently critically ill, has been invariably good. Of particular interest are the results of the follow-up examinations made from six months to sixteen years after the initial attack. There have been four

mild recurrences in three patients but complete recovery, without sequelae, has occurred in every instance. A similar experience has been reported from the Mayo Clinic[4] in a series of patients followed for periods ranging from one to eight years. It seems probable that this is not a disease which later in life appears as constrictive pericarditis.

SUMMARY

An analysis has been made of the clinical features in twenty-seven patients with acute serofibrinous pericarditis of undetermined etiology. It is important to distinguish this type from others having a more serious prognosis, particularly those associated with myocardial infarction, tuberculosis or rheumatic fever. Although the cause is not known, it seems possible that in many cases it is a virus; in some instances pericarditis may represent an immune reaction to bacterial invasion of the throat or sinuses.

An infection of the upper respiratory passages or pneumonia of the primary atypical variety preceded pericarditis in twenty-three of the twenty-seven patients. The course was variable in severity and duration but the prognosis for recovery was always good. Shock or congestive failure was not observed. Cardiac enlargement apparently was due to a greater extent to dilatation than to effusion into the pericardial sac. Pleural effusion was present in fourteen cases. The occurrence of fever, a friction rub and an increase in the sedimentation rate of the erythrocytes on the first day of illness were aids in differentiating this type of pericarditis from that following cardiac infarction. Serial electrocardiograms were usually diagnostic. Transient cardiac irregularity due to premature contractions was recorded in three patients. It is noteworthy that prolongation of the P-R interval, frequently seen in acute rheumatic fever, was not observed. Recurrences, milder than the original attacks, occurred four times in three cases.

Penicillin, streptomycin and sulfadiazine exerted no manifest beneficial effect on the pericarditis. Aureomycin, because of its antiviral action and in the light of recent favorable results observed in the treatment of primary atypical pneumonia, is worthy of trial.

Follow-up examinations, made at intervals ranging from six months to sixteen years after the original illness, showed complete recovery without sequelae in every instance. It appears unlikely, therefore, that this disorder is the precursor of constrictive pericarditis.

For permission to use the records of private patients we are indebted to Drs. Dana W. Atchley, Frederick R. Bailey, Ralph H. Boots, Norton S. Brown, Henry A. Cromwell, Putnam C. Lloyd, Howard F. Shattuck, Martin deF. Smith and Sidney C. Werner, of New York City, and Dr. G. Barton Barlow, of Englewood, N. J.

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Infrapulmonary Pleural Effusion Simulating Elevation of the Diaphragm*

EMIL ROTHSTEIN, M.D. *and* FRANCIS B. LANDIS, M.D.
Wood, Wisconsin

THE collection of pleural fluid—exudate or transudate—between the diaphragm and the inferior surface of the lung so as to simulate diaphragmatic elevation is an infrequent occurrence. Because of the concave shape of the lung base the fluid assumes a convexity superiorly and resembles the appearance of an elevated diaphragm in the standard postero-anterior roentgenogram. The lateral costophrenic sinus is often sharp and clearly outlined. When examined by means of the fluoroscope the infrapulmonary effusion usually moves synchronously with the diaphragm. Occasionally a fluid wave may be transmitted through the effusion synchronously with the heart beat.[1]

Rigler[2] described two cases of infrapulmonary effusion in 1931. One was due to nephrosis in a child and was associated with edema; the other was due to metastatic carcinoma. In other publications[3] he added to the ease of diagnosis of this condition by his demonstration that fluid shift may occur when the patient is placed in different positions. He emphasized the diagnostic value of the right and left lateral decubitus, recumbent and Trendelenburg positions and showed that the location of the fluid was often markedly influenced by gravity. We must disagree, however, with his view that these are usually transudative in character for our own experiences as well as those of other authors indicate that infrapulmonary effusions are commonly exudative in etiology. Katz and Reed[4] report a higher incidence of exudates with high specific gravity and protein content. Yater and Rodis[1] in 1933 reported infrapulmonary effusion due to tuberculous pleurisy; it shifted with posture changes. Autopsy revealed thin fibrinous pleural adhesions. Parsonnet et al.[5] described three cases, one of which was studied at autopsy; free fluid was found but no evidence of fluid encapsulation. They also demonstrated the value of pneumoperitoneum as a diagnostic aid.

We have had the opportunity to study twelve cases of infrapulmonary effusion. Six of these occurred during the course of pulmonary tuberculosis. Two are of unknown etiology, one is due to bronchogenic carcinoma, one is cardiac, one is a postpneumonic empyema and one is due to metastatic hypernephroma. Brief histories of several typical cases follow.

CASE REPORTS

CASE I. Known pulmonary tuberculosis had existed with relatively normal lower lung fields, as seen on an x-ray of December 1, 1947 (not shown). Left chest pain led to a new film taken December 31, 1947, (Fig. 1) which disclosed an apparent idiopathic left diaphragmatic elevation. Close observation revealed the air-filled colon in a normal position, yet approximately 2 inches below the upper level of the opaque density. Thoracentesis revealed a clear yellow exudate. X-ray ten days later (Fig. 2) showed a massive left pleural effusion.

CASE II. Known pulmonary tuberculosis with left pleural effusion had existed from June, 1947. X-ray on September 23, 1947, (Fig. 3) revealed an apparent elevation of the left dia-

*From the Veterans Administration Hospital, Wood, Wisconsin, Tuberculosis Division. Published with permission of the Chief Medical Director, Dept. of Medicine and Surgery, V.A., who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

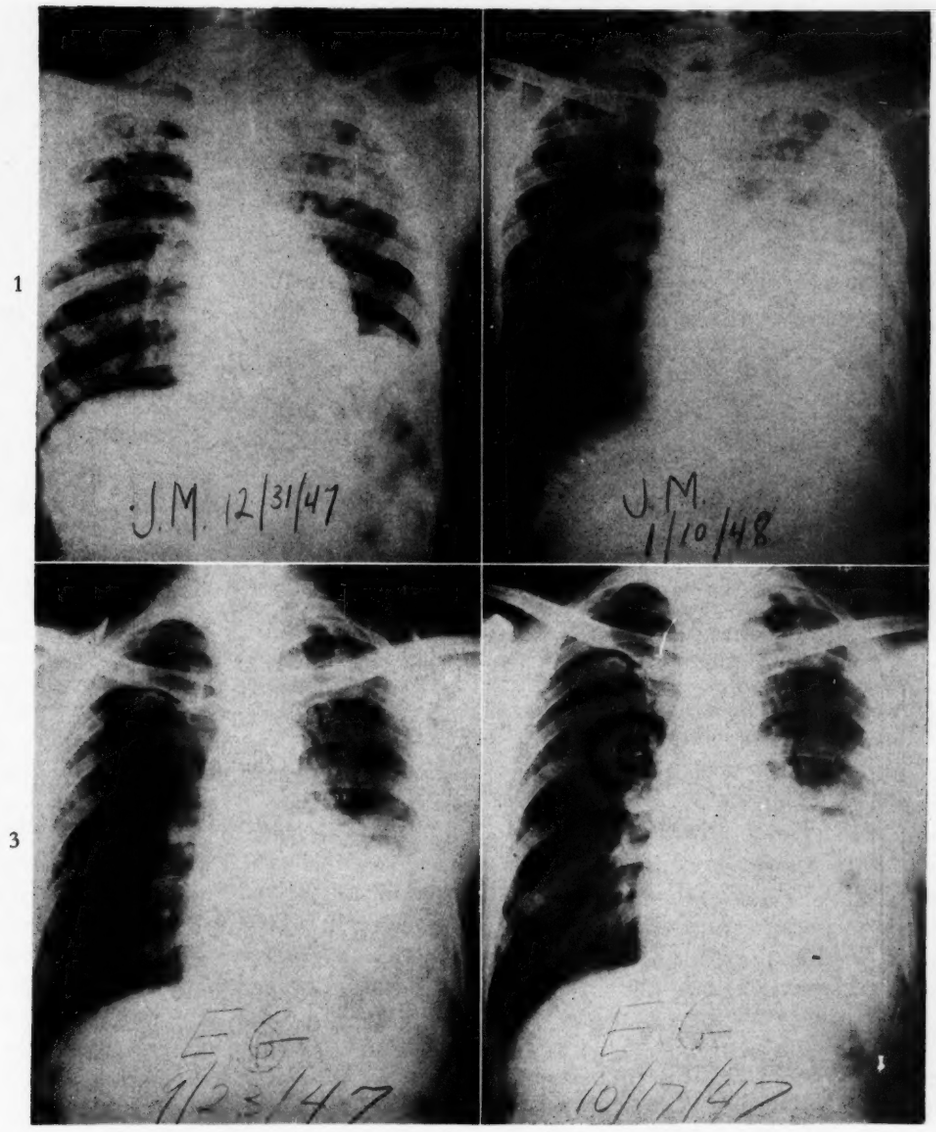

FIG. 1. Advanced bilateral pulmonary tuberculosis is present. There is an apparent elevation of the left diaphragm. However, the air-filled colon can be seen in its usual location several inches below the apparent diaphragmatic shadow. Thoracentesis on same day revealed clear straw-colored fluid. (Case I.)

FIG. 2. Same case as Figure 1 ten days later. A general pleural effusion is now present indicating that pleural adhesions were probably not responsible for the infrapulmonary localization.

FIG. 3. Pulmonary tuberculosis is present in the left lung. In addition there is apparent elevation of the left diaphragm to the eighth rib posteriorly. However, the stomach bubble can be clearly visualized in the left upper quadrant of the abdomen. (Case II.)

FIG. 4. After thoracentesis with removal of pus and air replacement. An air bubble can be seen within the infrapulmonary effusion. Encapsulation in this case prevented the air from rising to the apex of the thorax. (Case II.)

phragm. The stomach bubble could be clearly seen 3 to 4 inches below the apparent phrenic level. Figure 4 taken after thoracentesis illustrates an air pocket in the infrapulmonary region. In this case the fluid was encapsulated, thus explaining its localized position.

CASE III. Pulmonary tuberculosis was known to exist. Chest x-ray on October 30, 1947, (Fig. 5) showed an apparently elevated left diaphragm. In addition, mediastinal and interlobar effusions could be seen. On fluoroscopy the convex shadow at the left base moved freely with respiration. In addition the stomach bubble was visualized in its normal position, yet about

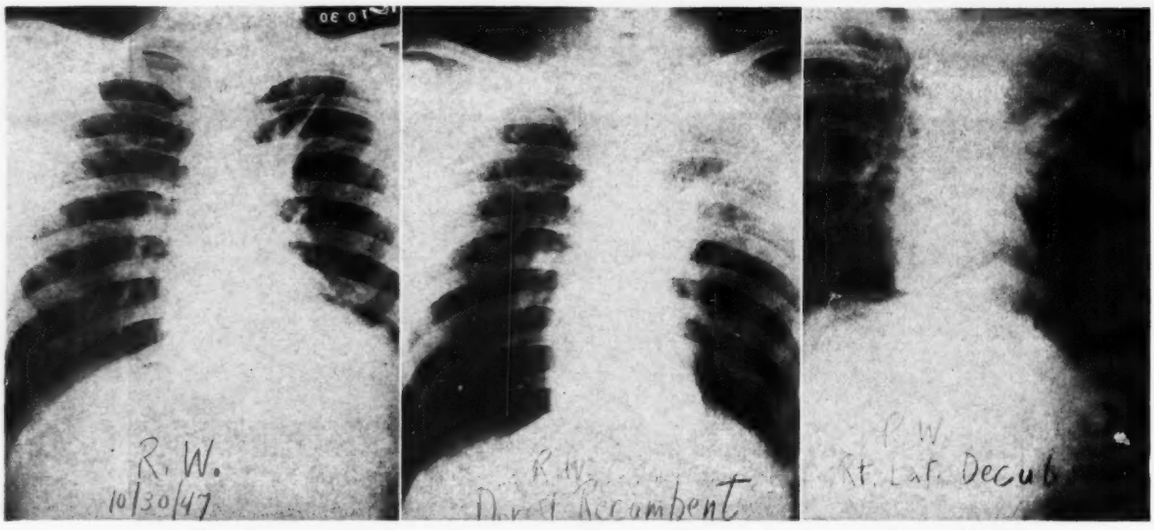

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FIG. 5. Bilateral tuberculosis is present. The left diaphragm is apparently elevated. In addition there are evidences of mediastinal and interlobar collections of fluid. On fluoroscopy the left "diaphragm" moved very readily with respiration. Thoracentesis revealed clear yellow fluid. (Case III.)

FIG. 6. Case III on same day with patient in dorsal recumbent position. The two diaphragms can be seen in their normal positions. The fluid has now gravitated to the apex of the lung indicating that its infrapulmonary location was not due to encapsulation.

FIG. 7. Patient lying on his right side. The fluid has now collected in the mediastinal region, particularly in the upper portion. (Case III.)

2 inches from the upper surface of the convexity. When the patient was placed upon a tilt table and this was lowered, the fluid could be seen to move freely about the chest, readily leaving its infrapulmonary location. This was especially marked when the patient was placed in the Trendelenburg position. This is illustrated in Figure 6 which demonstrates how the fluid has gravitated to the pulmonary apex and the true position of the left diaphragm can be seen. On placing the patient erect the infrapulmonary effusion reappeared at once. In the right lateral decubitus position (Fig. 7) the fluid lay along the mediastinum and both leaves of the diaphragm may be seen to be equal. In the left lateral decubitus (not illustrated) the fluid sought a level along the lateral costal gutter. Thoracentesis showed a clear straw-colored fluid. Subsequent films revealed that the fluid increased and assumed the configuration usually seen in pleural effusions.

CASE IV. Pulmonary tuberculosis was known to exist. An x-ray on May 31, 1948, (not shown) indicated normal lung bases and diaphragms equal in position. Figure 8 taken on June 12, 1948, showed apparent elevation of the right diaphragm. There were no concomitant symptoms. It is of interest that this effusion developed while the patient was receiving streptomycin treatment (1 Gm. daily). As in Case III the fluid was freely mobile, changing position readily with the patient on the tilt table or erect. When the patient leaned to either side the fluid readily ascended the lateral or medial chest wall. The "pseudodiaphragm" moved quite freely. Figure 9 illustrated the dorsal recumbent position with the fluid spread over the right posterior chest. Figure 10 showed the free shift of fluid to the right costal gutter in the right lateral decubitus position. On deep prolonged expiration the fluid could be seen ascending the right lateral chest wall. Injection of 100 cc. of air did not change the appearance of the infrapulmonary effusion. The air could not be visualized. Right intrapleural pressures were taken with the patient lying on the left (uninvolved) side. They were −9 and −6 cm. of water which can be considered within the range of normal. Thoracentesis showed a clear yellow fluid with a specific gravity of 1018. There were 300 cells, 97 per cent lymphocytes and 4 Gm. of protein per 100 cc.

Two other cases were diagnosed in tuberculous patients. One of these was spontaneous and the other was apparently due to trauma during the first stage of thoracoplasty. This last patient was, like our fourth case, receiving streptomycin therapy.

One patient with an acute myocarditis

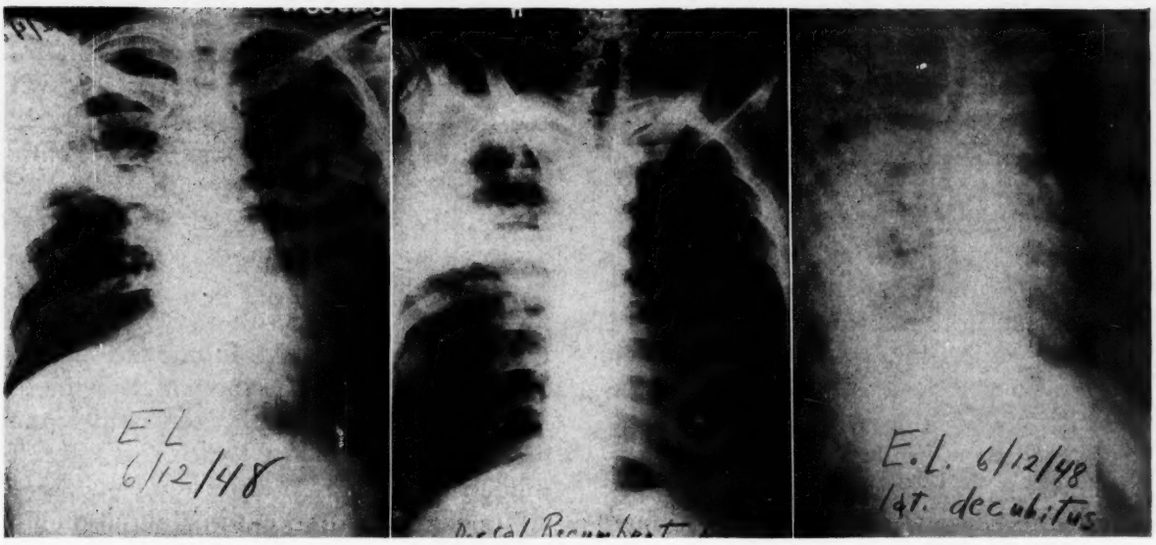

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FIG. 8. Case IV. Illustrated are advanced bilateral pulmonary tuberculosis and an apparent elevation of the right diaphragm. X-ray two weeks earlier (not shown) showed both diaphragms equal but otherwise identical. Thoracentesis on June 12, 1948, revealed clear yellow fluid. Intrapleural pressures −9, −6. Fluid shifted readily with various movements of the body.

FIG. 9. Same case as Figure 8 with patient lying on his back. X-ray made one to two minutes after Figure 8. Both diaphragms are seen to be in their normal positions. The fluid has accumulated over the right upper lobe indicating that its original location was not due to encapsulation. A radiologically normal right lower lobe can be visualized.

FIG. 10. Same case as Figure 9 a few minutes later with patient lying on his right side showing that the fluid move freely in the pleural space. As he stood erect the fluid instantly reassumed the distribution shown in Figure 8.

developed an infrapulmonary effusion as an incident in his decompensation. It resolved spontaneously. An eighth case occurred in a patient with encapsulated empyema following pneumonia. Here the presence of a large collection of pus was proven by surgical exploration. The lung was widely adherent and the empyema was encapsulated between the right leaf of the diaphragm and the base of the lung. Mediastinal encapsulated empyema was also present.

A ninth case was secondary to pleural and pulmonary metastases from a hypernephroma. Features of this case were (1) mobility of the fluid and (2) demonstration of the left diaphragmatic level by use of citrocarbonate orally; this filled the stomach with gas and delineated the infrapulmonary effusion more clearly.

The tenth case occurred in a patient with a superior vena cava obstruction due to bronchogenic carcinoma. It was associated with diaphragmatic paralysis as proven by paradoxical (upward) movement during sudden deep inspiration (the so-called sniff test). Along with the right basal convexity a minute interlobar effusion was seen in the fissure of an inferior accessory lobe.

Two cases were of unproven etiology. One was apparently secondary to pneumonitis of unknown etiology (lung abscess or infected cyst may have been present) while the other appeared idiopathically and may eventually prove to be tuberculous. These were both freely mobile and were well demonstrated on dorsal recumbent and lateral decubitus films.

COMMENT

Pleural effusions may assume a variety of configurations. Most common is that of a curvilinear density, with concavity downward and outward extending up along the axillary border of the chest. This is confirmed on physical examination as the "curved line" of Damoiseau and the "S" line of Ellis. Effusions in excess of 300 to 400 cc. usually obliterate the costophrenic sinus on the erect postero-anterior film and roll up the lateral costal gutter in the lateral decubitus position. Smaller effusions may

occupy the posterior costophrenic sinus and usually are not seen on standard postero-anterior exposures. They may be visualized on oblique projections or in lateral decubitus positions. Transudates and the majority of exudates, excepting empyemas and long-standing encapsulated effusions, show free movement on posturing the patient in various tilted or horizontal positions.

The configuration of a typical effusion is dependent upon four physical factors: (1) hydrostatic pressure of the fluid; (2) retractility of the lung which maintains the normally negative intrapleural pressure; (3) capillarity which is dependent upon the cohesive force between the pleural surfaces and the fluid; (4) physical properties of the fluid itself such as surface tension, etc. The hydrostatic pressure is dependent upon the force of gravity and the specific gravity of the fluid. There is no proof that the latter is ever sufficiently altered to influence the location of atypical pleural effusions. Such unusually situated collections may occur with transudates as well as with blood, pus, etc. The force of gravity, if it acted alone, would compel all effusions to rest directly upon the diaphragm with the lung floating upon them. The retractility of the lung tends to draw all parts of the lung more or less equally toward the hilum and its effects are most clearly seen in the presence of pneumothorax. It is impaired in the presence of pleural adhesions or in the presence of pulmonary disease such as consolidation, fibrosis, etc. Capillarity plays little or no part in the localization of effusions since it is only in play when the pleural surfaces are apposed or within a few millimeters of each other. There is no evidence that the surface tension, viscosity or other physical properties of the fluid play any part in its configuration; and since the force of gravity is constant, changes in retractility of the lung, as influenced by its elasticity and by pleural and pulmonary changes, are the chief or only additional factors in determining the localization of pleural effusions. This, partly counterbalanced by the weight of the fluid, is the predominant force responsible for the curvilinear configuration of the usual effusion. When air or other gases are present with the fluid in the pleural space, gravity becomes an even greater determining force and a horizontal fluid level results, although retractility still plays a part in the shape assumed by the lung.

When the pathogenesis of abnormal effusions is considered, altered retractility is the usual factor present. Pulmonary fibrosis, consolidation, edema and emphysema by reducing the pulmonary retractility may permit the effect of gravity to exert a greater influence. Changes in the pleura due to old adhesions or more recent inflammation help to determine the site of an effusion.

The convex upper border of infrapulmonary effusions has never been adequately explained. Korol and Scott[7] postulated hydropneumothorax, "the veiled air bubble," as a cause, with the air pocket obscured by a partly adherent and expanded lung. We have been unable to find this condition present in any of our cases despite detailed study of many films and many fluoroscopic examinations; other authors have also come to the same conclusion. Postmortem examinations have suggested fortuitously situated pleural adhesions as the cause in some instances. In a number of our cases the fluid was proved to be encapsulated by its failure to shift with changes in position and one case was found to be adherent when an infrapulmonary empyema was drained surgically. On the other hand, we did find a free shift in the fluid in nine of the twelve cases and in several of these lateral decubitus films revealed a quite free pleural space. In six the fluid could be seen to shift quite readily upon fluoroscopic examination; yet when the erect position was assumed, the fluid immediately returned to its infrapulmonary location. In addition, upon deep forced expiration the fluid can in some instances be forced up along the axillary chest wall (first described by Cincotti et al.[6] and confirmed by us). This was not associated with pain or other evidence of trauma to pre-existing adhesions.

It would logically appear that factors altering lung retractility should be of considerable importance in localizing this atypically distributed fluid. Yet in five of our cases the lower one-half of the lung was seen to be normal, at least radiologically, prior to the development of the effusion. In one of these normal intrapleural pressures (−9, −6 cm. of water) were obtained on the involved side while the fluid was present and this, too, would speak for normal elasticity of the underlying lung. These factors militate against the theory that decreased or increased retractility is responsible for this unusual distribution. Having ruled out altered capillarity and unusual physical features of the fluid in all cases, and pleural adhesions or disease of the underlying lung in several, we must state that no solution can be offered here to explain the basic cause of this configuration. It may be of some importance that infrapulmonary effusions are at least occasionally associated with other atypical collections. Of our twelve cases two were associated with mediastinal collections of fluid and three with interlobar effusions. We are unable to state the exact significance of this finding. It is also worthy of note that the convex upper border of infrapulmonary effusions is not always present. The upper border may be flat or irregular. (None of the cases in this series falls in that category, however.)

In the diagnosis of infrapulmonary effusions undoubtedly the most important feature is a high index of suspicion. It is often if not usually the case that the basal convex density is thought to be an elevation of the diaphragm. Our first procedure in a case of this type is a careful study of consecutive x-ray films. In several instances the sudden appearance of an unexplained "elevation of the diaphragm" in a patient whose earlier films showed no such change was clarified by the additional finding of the development of minimal blunting of the costophrenic angle. In one case a small, newly developed supradiaphragmatic triangle of opacity was analyzed as a small interlobar effusion extending into a right inferior accessory interlobar fissure. An infrapulmonary effusion would, of course, be in direct contact with such a fissure, which normally opens upon the diaphragm. When the left chest is involved, the stomach or colon may contain gas and by their position give a clue to the true level of the diaphragm. As a diagnostic procedure of some value we have used 2 dr. of citrocarbonate to outline the stomach. If this is dissolved and swallowed at once, the gas-filled stomach silhouette outlines the inferior surface of the left diaphragmatic leaf very well. Other agents, such as a Seidlitz powder or carbonated beverage may be just as effective. In cases of infrapulmonary effusion a concavoconvex density of varying thickness will be seen between the gas-filled stomach and the lung. This finding, while suggestive, may be simulated by subphrenic abscess. We encountered one case of large infected basal lung cyst the nature of which was not revealed by this procedure.

Fluoroscopic examination of these cases is valuable and often reveals the exact nature of the density under study. Diaphragmatic motion is usually well transmitted to the overlying fluid and its presence is of great value in ruling out phrenic paralysis and subphrenic abscess. The movements of the diaphragm were well made out in each of the six cases studied in this manner. When the patient is postured, a definite shift of the fluid is noted in most cases. In our work we lean patients as far to each side as possible and study the silhouette for evidence of change in the configuration of the density. In each of our cases so studied positive proof of pleural effusion has been obtained in this fashion. Long-standing encapsulation, however, would invalidate this particular method. With the patient supine or in the Trendelenburg position the two leaves of the diaphragm may become equal (Fig. 6) while the involved side becomes diffusely more opaque than previously, due to a shift of the fluid along the posterior chest wall.

X-ray studies made in different positions

are of great value. These include chiefly dorsal recumbent and lateral decubitus films. A word of caution is necessary about the latter. Unless the patient's body is blocked up for at least 3 inches the fluid ascending the axillary portion of the chest may be lost to view by being cut off the film.

Pneumoperitoneum is very helpful in revealing the true position of the diaphragm, particularly upon the right side. Sante[8] has shown this to be harmless even in the presence of subphrenic abscess. As a rule 200 to 400 cc. of air is quite adequate. It was of great value to us in two cases in which a differential diagnosis between an encapsulated empyema or effusion and a high diaphragm was resolved in favor of the latter by diagnostic pneumoperitoneum.

Thoracentesis provides proof positive of an effusion. Yet it may be unsuccessful if the fluid is pocketed and so deeply situated as to be inaccessible. Subphrenic or intrapulmonary collections may be aspirated and mistaken for pleural effusion.

In the differential diagnosis we have encountered elevation of the diaphragm most frequently. This may be due to previous phrenic paralysis, re-expanded pneumothorax, subphrenic disorder, eventration or recent acute inflammatory supradiaphragmatic disease. Other conditions which may be confused include subphrenic abscess, hepatomegaly and diaphragmatic hernia. Tumors of the lung, mediastinum and pleura, large basal lung cysts and atelectasis must also be considered. The use of pneumoperitoneum to establish the position of the diaphragm will usually prove the supra- or infradiaphragmatic position of the disputed density while thoracentesis or even exploratory surgery will be needed in the case of deep-seated encapsulated collections.

Nothing need be said about treatment. The etiology is the same as that of other effusions and the treatment is that of the underlying condition.

SUMMARY AND CONCLUSIONS

Twelve cases of infrapulmonary effusion have been studied. This condition is not rare but is frequently overlooked. Its etiology is the same as that of other pleural effusions. The exact cause of the atypical location is not known. The diagnosis and differential diagnosis are discussed.

We are indebted to Drs. Wilson Weisel, Mark Garry and Jerome Marks for permission to include cases originally seen by them:

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Prognosis in Arterial Hypertension*

Comparison between 251 Patients after Sympathectomy and a Selected Series of 435 Non-operated Patients

SVEN HAMMARSTRÖM, M.D. *and* POUL BECHGAARD, M.D.

Stockholm, Sweden *Aarhus, Denmark*

THE beneficial effects of neurosurgical treatment of hypertension have been fully proved by several reports on its effects on blood pressure, hypertensive retinopathy, cardiac function and subjective symptoms.[5–16] But in spite of the large clinical experience with neurosurgical treatment information as to its effect on life expectancy is limited due to the difficulty "to find comparable data in the literature concerning the prognosis for hypertensive patients treated medically or untreated."[15]

Peet and Isberg[3] have shown that dorsal ganglion- and splanchnicectomy changed the survival rate after more than five years in malignant hypertension from less than 1 to more than 20 per cent. They used the Keith, Wagener and Barker[4] figures as controls. Smithwick[15] compared the survival rate in the same controls with his own series of 256 hypertensives followed five to nine years after lumbodorsal sympathectomy. The prognosis was better in all groups of the surgically treated patients. The difference observed was statistically significant for groups II, III and IV. In groups III and IV the survival rates in the operated series comprising seventy and thirty-nine patients, respectively, was 70 and 75 per cent as compared with 9 and less than 1 per cent in the non-operated series of 37 and 146 patients, respectively. Groups I and II of Keith, Wagener and Barker include ten and twenty-six patients, figures too limited for conclusions regarding the life expectancy in these groups.

One of us (Bechgaard)[1] has followed-up a series of 1,000 non-operated hypertensive patients. Neither this nor any other unselected series is suitable for comparison with operated groups which are selected according to certain rules. This is demonstrated by the fact that retinal exudates occurred in only 1 per cent of Bechgaard's series and in 31 per cent of the present series of operated patients.

In Bechgaard's series the mortality rate in men was twice as high as in women. In patients with signs of myocardial damage by ECG the mortality figure was 547 as compared with 207 in hypertensives without such changes and 100 in the average population of the same age groups.

The present series of 251 operated patients has been followed two to eight years after sympathectomy. It includes all hypertensives operated on at the Neurosurgical Clinic of the Serafimer Hospital in Stockholm from February, 1940 to August 1946, with the exception of three patients who have not been traced. Five patients in the whole series died in consequence of the operation. Since 1943 there has been no operative mortality in a consecutive series of 250 hypertensives. One hundred forty-eight patients have been submitted to bilateral lumbodorsal ganglion- and splanchnicectomy from Th_9 or Th_{10} to L_1 according to Smithwick; of these twenty-four later died. Sixty-four patients were operated on bilaterally according to Peet; of these thirteen died. Thirty-one were operated on only

* From the Neurosurgical Clinic of the Serafimer Hospital and the IVth Medical Service of St. Erik's Hospital, Stockholm, Sweden, and from the Municipal Hospital II Division, Copenhagen, and Amtssygehuset, Medical Service, Aarhus, Denmark.

one side and eighteen of them are dead. Most of the patients with unilateral sympathectomy were in a poor state before the operation. For a description of the criteria used by us in the selection of patients for sympathectomy the reader is referred to Hammarström[2] and a more detailed investigation which is to be published by us this year.

TABLE I
DISTRIBUTION OF AGE IN VARIOUS GROUPS OF 435 NON-OPERATED AND 251 SURGICALLY TREATED HYPERTENSIVES

	Group IV		Group III		Group II	
	Operated	Not Operated	Operated	Not Operated	Operated	Not Operated
No. of Cases	77	94	88	177	86	146
	Per Cent					
Age						
0–29	9	1	4	...	9	2
30–39	16	15	18	5	27	16
40–49	54	41	50	38	47	35
50–59	21	35	27	47	17	40
60–65	...	3	1	10	...	7
	100	100	100	100	100	100

The non-operated series was selected according to the same rules as the patients operated on and followed-up two to ten years. In this series 95 per cent, 435 patients, were traced. They have been collected (some of them by Dr. Soegaard)[17] from about 130,000 records from various hospitals in Copenhagen and the St. Erik's Hospital in Stockholm.

The age distribution is seen in Table I. The distribution of blood pressure at the first examination is seen in Table II. The average age of the patients was slightly lower in the operated than in the non-operated group (43.0 and 49.6 years). In all groups of the operated series a greater percentage showed higher systolic and diastolic levels than the non-operated.

We have divided our material into four groups; men and women are treated separately. The first group of patients was not included in this study as it contained those with uncomplicated hypertensive disease without marked subjective symptoms. Patients with such benign hypertension are not selected for sympathectomy. The life expectancy of this group has been indicated by Bechgaard.[1] Group II includes those with marked subjective symptoms but without signs of myocardial damage. They may show left axis deviation in the ECG and/or a relative enlargement of the left ventricle if the heart volume is within normal limits according to teleradiography. The retinal changes in the patients in our second group are classified as group I or II according to Keith and Wagener. Group III includes those with the same eyeground changes or, in addition, retinal hemorrhages with or without signs of thrombosis of the retinal vessels. Patients in group III further show one or more of the following signs of cardiovascular damage: negative T_1 in the ECG, heart volume above the predicted normal (500 ml./M.^{2} body surface in men and

TABLE II
DISTRIBUTION OF BLOOD PRESSURE AT FIRST EXAMINATION IN 435 NON-OPERATED HYPERTENSIVES AND BEFORE OPERATION IN 251 SURGICALLY TREATED PATIENTS

	Group IV		Group III		Group II	
	Operated	Not Operated	Operated	Not Operated	Operated	Not Operated
No. of Cases	77	94	88	177	86	164
	Per Cent					
Systolic Pressure						
<200	...	7	2	8	10	23
200–215	5	16	15	26	23	34
220–235	17	23	22	30	26	21
240–255	25	31	25	21	28	12
260–	53	23	36	15	13	10
	100	100	100	100	100	100
	Per Cent					
Diastolic Pressure						
<110	...	1	1	7	6	5
110–125	1	15	9	34	25	43
130–135	12	16	9	13	20	27
140–155	55	56	58	41	42	23
160–	32	12	23	5	7	2
	100	100	100	100	100	100

450 ml./M.^{2} in women, or the transverse diameter of the heart greater than one-half the inner thoracic diameter), residual damage after cerebral insult and constant albuminuria. In group IV we include all hypertensives with definite retinal exudates and/or papillary protrusion since we found the life expectancy to be about the same if the patients in this group did or did not have papillary protrusion.

Patients with cardiac decompensation at rest, auricular fibrillation, myocardial infarct or renal insufficiency were not included in the non-operated series. A few patients in the operated series had cardiac insufficiency and were compensated with digitalis before operation while another minor group showed renal insufficiency before operation. All of them died, mostly within a year after operation.

In the patients with primary malignant hypertension in the control series the time of observation was counted from the date of their first symptoms even if the retinal exudates were first observed later. In the operated series the time of observation was always counted from the operation. This method of calculation gave a higher significance to the difference between the operated and non-operated patients than is shown by the figures.

The period of observation has been divided into one-year intervals. The mortality rate is calculated by dividing the

TABLE III

COMPARISON OF PROGNOSIS IN 453 UNOPERATED HYPERTENSIVES AND 251 HYPERTENSIVES AFTER SYMPATHECTOMY

Group	IV		III		II	
	Men	Women	Men	Women	Men	Women
Unoperated No. of cases	69	25	83	94	42	122
Deaths	68	24	57	44	9	21
Mortality rate (per mille)	307	330	181	80	41	20
Operated no. of cases	38	41	35	50	29	58
Deaths	18	16	9	8	4	0
Mortality rate (per mille)	150	96	52	33	25	
Error of mean of differences (per mille)	80	115	56	37	42	45
Significance of differences of means in unoperated and operated patients (per cent)	93.5	98	98	59.3	30	

TABLE IV

RATE OF SURVIVAL IN VARIOUS GROUPS OF OPERATED AND NON-OPERATED HYPERTENSIVES*

Years of Observation	Group IV				Group III				Group II			
	Men		Women		Men		Women		Men		Women	
	Operated	Not Operated	Operated	Not Operated	Operated	Not Operated	Operated	Not Operated	Operated	Not Operated	Operated	Not Operated
0	100	100	100	100	100	100	100	100	100	100	100	100
1	76	67	90	72	95	83	90	96		93		98
2	61	42	78	56	86	67	88	86		87		98
3	55	22	75	36	84	55	85	80		85		94
4	53	15	64	16	81	44	85	76		80		93
5	48	15	51	12	78	38	82	70		78		90
6	46	6	39	4	72	30	82	65		75		85
7	35	4	32	4	67	25	80	56		73		84
8	32	3	20	4	64	19	78	51		70		83
9	27	3	15	0	58	16	76	48		65		80
10	24	1	10	0	56	13	72	45		60		78

* The figures indicate the percentage of survivals. Prognosis in operated patients in group II cannot yet be calculated.

number of dead during each year by the number of persons in the group at the beginning of the year which indicates the probability of death within one year expressed per thousand.[1]

The results of comparison between the operated and the control patients are shown in Table III. The prognosis is consistently better in the operated than in the non-operated patients. In patients with retinal exudates (group IV) this difference is statistically significant in both sexes. In this as in other series of hypertensives the frequency of malignant hypertension is higher in men than in women (36 against 17 per cent). In the unoperated series in group IV the prognosis is about equally poor in men as in women.

In groups II and III the mortality rate is more than twice as high in men as in women. In men with signs of cardiovascular damage (group III) the prognosis is significantly better in the operated than in the control series. The significance of the lower mortality rate in the operated women in group III compared with the controls in this group is less pronounced, but it is still 60 per cent.

In group II the life expectancy is favorable and we need a longer follow-up time to decide if the neurosurgical treatment significantly improved the prognosis. With a longer period of observation, the difference may be conclusive since we already have nearly twice as high a mortality rate in the male controls as in the operated series and no mortality among fifty-eight operated women against twenty deaths in 122 controls.

In Table IV we have calculated the probable duration of life in the various groups of controls and operated patients. The figures indicate the percentage of survivals after various years of observation.

SUMMARY

Our data demonstrate the beneficial effect of sympathectomy on life expectancy in patients suffering from essential hypertension.

A new classification of essential hypertension, based on the clinical findings which have proved to be of greatest prognostic value, is proposed.

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Study of the Coagulation Mechanism of Pleural Blood in Hemopneumothorax*

STUART W. COSGRIFF, M.D.
New York, New York

THE remarkable fluidity of blood obtained from the relatively intact pleural cavity by thoracentesis or at postmortem examination has suggested that the mesothelial pleural membranes, if intact as regards external opening and if not grossly traumatized, may act toward blood in a manner similar to the untraumatized endothelium of blood vessels or extravascular receptacles coated with silicone, paraffin or collodion.[1]

It has been possible to obtain fluid gross blood on successive thoracenteses particularly in cases of spontaneous hemopneumothorax.[1] In the autopsy reports on this condition[2,3] the blood in the pleural cavities was completely unclotted or was fluid containing some clots. In Pitts' original report[4] he noted a large amount of fluid blood in the pleural cavity together with "three handfuls of clots." A massive amount of free fibrin has been reported in only one case[4] and note was made of histologic evidence of fibrin deposition on the pleural surfaces in one other case.[3]

Pitts[4] referred to the observations of two investigators[6,7] concerning the state of coagulation of blood in the pleural cavity. Thus Trousseau[6] found that blood injected (without aseptic precautions) into the pleural cavity of a horse clotted within five minutes of injection. This investigator believed that the fact blood in the pleural cavity clotted even more rapidly than in external hemorrhage may well be ascribed to the agitation produced by the cardiorespiratory movements with rapid defibrination and deposition of fibrin on the pleural surfaces. However, fibrin has been observed in only a minority of the autopsied cases. Furthermore, Pagenstecher[7] believed the pleurae could keep blood in a fluid state but not unaltered, inasmuch as blood injected into the pleural cavity became incoagulable after six hours. Hartzell[1] cited the work of Sacquepee[8] that blood in the non-infected pleural space of man becomes incoagulable after contact with the pleural membranes for five or six hours.

This study was initiated to determine the state of coagulation of the pleural blood in a patient with a recent hemopneumothorax, with reference to the factors involved in the mechanism of blood coagulation.

CASE REPORT

H. D. (Unit No. 898805), a forty-two year old white male, was admitted to the Presbyterian Hospital because of progressively severe pleuritic chest pain and shortness of breath during the preceding twenty-four hours. The patient previously had been in excellent general health. Chest x-rays had been negative three and six years before. There was no past history of respiratory symptoms or of exposure to tuberculosis or other pulmonary disease.

One week prior to admission he had been struck quite forcibly in the right chest by a heavy package. Immediately following the blow he experienced pain in the right chest associated with sweating and dyspnea but recovered completely within a few minutes. Four days before admission he experienced a sudden recurrence of pleuritic pain and shortness of breath which gradually disappeared during the next twelve hours. On the day prior to admission the patient again became aware of even more severe

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, N. Y.

shortness of breath and pleuritic right chest pain which continued until hospital admission.

On examination the patient appeared to be acutely ill, pale and dehydrated. Rectal temperature was 99.6°F., pulse was 120 and respirations 36 per minute. Blood pressure was 74 mm. Hg systolic with an unobtainable diastolic pressure. The trachea appeared to be in the midline position but there was a marked lag of respiratory movements on the right. The right chest was hyperresonant to percussion anteriorly, particularly over the second right interspace. Fremitus and breath sounds were absent over the anterior and posterior right chest. The left chest and lung were normal. The heart was percussed 10 cm. to the left of the mid-sternal line in the fifth and sixth interspaces. Heart sounds were of good quality. No clubbing nor cyanosis of the extremities was present.

The hemoglobin was 12.5 Gr. per cent; the red blood cell count 3,190,000 per cu. mm.; and the leukocyte count 16,690 per cu. mm. with 89 per cent polymorphonuclears. The venous blood hematocrit was 33.9; plasma specific gravity 1.0266; and total plasma proteins were 7.3 Gr. per cent. X-rays of the chest showed a hydropneumothorax on the right, with fluid reaching approximately to the level of the fourth rib anteriorly. The right lung was completely collapsed. A slight shift of the trachea and heart to the left was evident.

Thoracentesis of the right chest was performed within an hour of admission, with removal of 750 cc. of grossly bloody fluid. There seemed to be no excess tension in the pleural cavity. During this procedure the general condition of the patient improved greatly, the blood pressure increased to 110/70 and respirations slowed from 36 to 24 per minute. The blood removed by thoracentesis contained 10 Gr. per cent of hemoglobin and 1,800,000 red blood cells per cu. mm. The hematocrit of this specimen was 30.5, plasma specific gravity 1.025 and total proteins 6.5 Gr. per cent. Ten hours after admission the patient was comfortable, his blood pressure was 108/70, respirations were 16 and pulse was 88 per minute.

On the second day repeated laboratory studies on the peripheral blood disclosed a hemoglobin concentration of 9.6 Gr. per cent, red blood cells 3,350,000 per cu. mm. and hematocrit 31.6. The electrocardiogram was within normal limits. Chest x-ray still showed the hydropneumothorax with the fluid level extending to the fifth rib anteriorly. There was a slight increase in the expansion of the right lung when compared with the chest x-ray taken on the preceding day.

Thoracenteses were performed on the second, fifth, sixth and twelfth day with removal of 850 cc., 150 cc., 200 cc. and 425 cc., respectively. The hematocrit of these thoracentesis fluids ranged from 31 to 34. Chest x-ray on the eleventh day revealed that 40 per cent of the right lung was still collapsed and the fluid level at the sixth rib anteriorly. During the first two weeks of hospitalization he was given three 500 cc. whole blood transfusions which raised his peripheral blood hemoglobin to 13.5 Gr. per cent. Inasmuch as satisfactory progress was being made under conservative management he was allowed home for uneventful convalescence.

MATERIALS AND METHODS

Blood was withdrawn from the pleural cavity by the usual aseptic thoracentesis technic on the first, second, fifth and twelfth days of the patient's hospital stay.

Coagulation time determinations were performed according to a modification of the Lee-White venous clotting time technic.[1] Four chemically-clean, 75 by 10 mm. test tubes, syringe and needle were rinsed with physiologic saline solution. One cubic centimeter of blood was gently placed in each tube. Clotting was considered to have occurred when the blood did not flow after the four tubes were completely inverted. Normal values range between five and twelve minutes.

Prothrombin time determinations were performed on whole plasma, according to the Link-Shapiro modification[10] of Quick's technic,[11] using 0.1 molar sodium oxalate as the anticoagulant, commercially supplied rabbit lung thromboplastin and 0.025 molar calcium chloride. The normal value in this laboratory with the technic employed is 14 (± 2) seconds. The per cent of normal prothrombin activity was determined from the saline dilution logarithmic prothrombin activity curve constructed according to Quick.[11] By this technic 14 seconds equals 100 per cent of normal prothrombin activity, 22 seconds equals 30 per cent and 45 seconds equals 10 per cent of normal prothrombin activity.

The erythrocyte sedimentation rate was performed according to the Westergren method,[12] using 0.5 cc. of 3.5 per cent sodium citrate as the anticoagulant for 2.5 cc. of venous blood.

Normal values are considered as a fall of less than 20 mm. in one hour.

The thrombin which was employed was a commercially supplied purified powder of bovine origin made into solution with physiologic saline so that 1,000 units (National Institute of Health) were contained in one cubic centimeter of solution.

The fibrinogen* was an 85 per cent pure product of bovine origin which was dissolved in physiologic saline so as to obtain a concentration of 400 mg. per cent.

Fraction† of normal human plasma was prepared from a lyophilized powder made into solution with distilled water so as to contain 200 mg. of protein in 5 cc. of solution.

Protamine‡ was used as a 1 per cent solution of protamine sulfate.

RESULTS

Hematocrit. On the second hospital day the hematocrit and plasma specific gravity of the hemathorax blood were 31.0 and 1.0239, respectively. The corresponding values for venous blood were 31.6 and 1.0241. (Table 1.)

Blood Coagulation Time. The blood removed by the first thoracentesis was still fluid after standing for twenty-four hours. When the coagulation time of the second specimen of pleural blood was performed according to the technic of the venous blood clotting determination,[11] coagulation did not occur in any tube during a twenty-four-hour period of observation. The venous blood clotting time of the patient was seven minutes.

Prothrombin Time. There was no end point observed up to ninety seconds (5 per cent of normal prothrombin activity) when a prothrombin determination was performed on the second hemothorax specimen. The prothrombin time test was repeated on the third specimen and no end point was noted up to as long as 360 seconds. In order to determine whether this prothrombin time of infinity represented a deficiency of the prothrombin complex from the pleural blood or whether the failure to observe an end point was due to the absence of fibrinogen, another prothrombin time determination was performed on the third hemothorax specimen after adding 10 mg. of fibrinogen to the blood-oxalate mixture prior to centrifugation. No end point was noted in this modified prothrombin test up to six minutes. These results indicate that the markedly elevated prothrombin time was due to an actual absence of prothrombin in the hemothorax specimen.

TABLE 1

RESULTS OF OBSERVATIONS ON THE BLOOD COAGULATION MECHANISM OF AN INDIVIDUAL WITH HEMOPNEUMOTHORAX

	Pleural Blood	Peripheral Blood
Hematocrit	31.0	31.6
Plasma specific gravity	1.0239	1.0241
Blood coagulation time (in minutes)	∞	7
Prothrombin time (in seconds)	∞	15.0; 15.1
Prothrombin time (in seconds) with added fibrinogen	∞	
Fibrinogen (mg. per cent)	0	500
ESR (mm. per hour)	2	43
Defibrinated ESR (mm. per hour)	3	2
Calcium (mg. per cent)	8.1	9.3
Thrombin	0	
Non-protein nitrogen (mg. per cent)	42	43
Anticoagulant activity	0	
Fibrinolytic activity	0	
Capillary fragility	.....	normal
Bleeding time (minutes)	.....	4.5

The venous blood prothrombin time on the second and fifth hospital days was 15.0 and 15.1 seconds, respectively.

Fibrinogen. The peripheral venous blood contained 500 mg. per cent of fibrinogen. The presence or absence of fibrinogen in the pleural blood was investigated in several ways. Fibrinogen was found to be completely absent from the pleural blood according to the method of Cullen and Van Slyke.[15]

No coagulation resulted following the mixing of 0.5 cc. (500 units) of purified thrombin solution with 0.5 cc. of pleural blood (third specimen).

This absence of fibrinogen was inferentially confirmed by a study of the erythrocyte sedimentation rate (ESR). The ESR of the venous blood on the second hospital day was 43 mm. in one hour. A defibrinated venous ESR was 2 mm. in one hour. The ESR of the second specimen of pleural blood was 2 mm. and after defibrination for fifteen minutes the ESR of this specimen was 3 mm. in one hour.

* Furnished through courtesy of Parke, Davis & Co., Detroit, Mich.

† Furnished through courtesy of the American Red Cross.

‡ Furnished through courtesy of Eli Lilly & Co., Indianapolis, Ind.

Calcium. The calcium content of the pleural blood was 8.1 mg. per cent. The venous blood calcium was 9.3 mg. per cent.

Thrombin. Thrombin was shown to be absent from the pleural blood by the failure of coagulation to occur following the addition of 0.5 cc. of the pleural blood to 0.5 cc. of purified fibrinogen solution (2 mg.).

TABLE II

OBSERVATIONS CONCERNING THE PRESENCE OF AN ANTICOAGULANT IN PLEURAL BLOOD

Specimen	Coagulation Time (min.)
A. Venous blood normal control #1 =	9
Normal venous blood = 0.1 cc. pleural blood =	11
B. Venous blood of normal control #2 =	5
2 cc. normal control blood + 2 cc. pleural blood =	5
1 cc. normal control blood +2 cc. pleural blood =	7
C. 0.1 cc. pleural plasma =	∞
0.1 cc. pleural plasma + 0.1 protamine sulfate =	∞
0.1 cc. pleural plasma +1.0 protamine sulfate =	∞
D. 2 cc. pleural blood =	∞
2 cc. pleural blood + 4 mg. Fraction I =	∞
2 cc. pleural blood +40 mg. Fraction I =	∞

Non-protein Nitrogen. The non-protein nitrogen (NPN) of the pleural blood on the third specimen was 42 mg. percent. The venous serum NPN was 43 mg. per cent.

Anticoagulant in Pleural Blood. The presence of an anticoagulant in the pleural blood which may have been responsible for maintaining its fluid state was investigated by the addition of pleural blood to normal venous blood. This resulted in no significant change of the venous clotting time of two normal individuals. (Table II, A and B).

Protamine has been shown to inactivate the anticoagulant activity of heparin and heparin-like substances *in vitro* and *in vivo*.[16–18] The absence of a heparin-like anticoagulant agent in the pleural blood was confirmed by the fact that the addition of protamine sulfate to samples of hemothorax plasma did not modify the incoagulability of the pleural blood specimen. (Table II, C.)

Nor did the pleural blood clot following addition of 20 mg. of the antihemophilic Fraction I (Table II, D), indicating that the incoagulability was not associated with lack of the essential antihemophilic globulin substance.

Fibrinolysin. Inasmuch as the fluidity of menstrual blood has been ascribed in part to excessive proteolytic activity which lyses fibrin,[17,18] investigation for the presence of increased fibrinolytic activity of the pleural blood was carried out. The addition of 0.5 cc. of pleural blood to 5 cc. of normal venous blood did not produce any appreciable increase in the rate of fibrinolysis after twenty-four, forty-eight or seventy-two hours when compared with a control specimen of the same blood.

Blood Coagulation Mechanism of the Peripheral Blood. The mechanics of blood coagulation of the peripheral blood of the hemopneumothorax patient were normal in all respects. (Table I.)

COMMENT

In this patient with hemopneumothorax the pleural blood failed to clot upon removal from the chest. The thoracentesis specimens were comparable in hemoglobin content, hematocrit and plasma specific gravity to the circulating intravascular blood. The "incoagulability" of the hemothorax fluid after thoracentesis was confirmed on several occasions. The essential constituents for coagulation of blood, i.e., prothrombin, thrombin and fibrinogen, were determined to be completely absent from the pleural blood specimens. Calcium deficiency was not the basis for the absence of clotting inasmuch as calcium was present in relatively normal and adequate amounts. Furthermore, the hemothorax plasma, when recalcified during the performance of the prothrombin determination, also failed to clot. It was not possible to demonstrate any form of anticoagulant activity in the pleural blood.

The absence of the essential factors for coagulation in the pleural blood of this patient indicates that coagulation had already occurred prior to thoracentesis. Clotting within the pleural cavity was followed presumably by the normal phenomenon of fibrinolysis or by the deposition of fibrin on the collapsed lung. However, no grossly excessive fibrinolytic activity was found in the pleural blood.

It has been postulated that the relatively intact pleural serous membranes might serve to keep the blood in a fluid state by

virtue of some special property of these serous surfaces or even by the secretion of an anticoagulant at the site of the hemorrhage. Although it is possible that in some cases blood in the untraumatized pleural cavity may remain actually unaltered as regards coagulation, the present study offers evidence that coagulation of blood does proceed within the pleural cavity. Factors involved might include thromboplastin liberated by virtue of breakdown of platelets, contact of the blood with foreign surfaces and the agitation produced by respiratory movements. This clotting may be followed by the natural proteolytic process of fibrinolysis or by defibrination with fibrin deposition on the lung surfaces. Thus, at least in this patient, the so-called "incoagulable" hemothorax fluid was in reality serum which contained a suspension of some of the formed elements of the blood.

SUMMARY

1. A patient with hemopneumothorax with recovery is reported, together with observations on the pleural and venous blood coagulation mechanisms.

2. The grossly bloody pleural fluid failed to clot after thoracentesis and was found to be completely devoid of prothrombin, thrombin and fibrinogen. No anticoagulant activity was demonstrated in the pleural blood.

3. It is concluded that coagulation of blood occurred within the relatively untraumatized pleural cavity by mechanisms similar to those involved in any extravascular hemorrhage.

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Review

Some Neglected Aspects of Cardiology*

Circulatory Function of the Respiration

WILLIAM S. MCCANN, M.D.
Rochester, New York

IT is the purpose in this paper to point out certain features of the inter-relations of the heart and lungs which are not generally appreciated and which have not yet been translated into clinical practice. We will concern ourselves with the manner in which the lungs may act as a check-valve capable of regulating the transfer of blood from the right ventricle to the left. Up to the present time most discussions of the venous input and the cardiac output as expressed in Starling's law of the heart have assumed a passive role of circulation through the lungs. The current explanations of the apparent discrepancies in the operation of Starling's law can be clarified by an understanding of this check-valve function of the lung. Furthermore, by means of this conception we can more readily understand the genesis of congestive failure of the circulation. We hope to show that the condition which is commonly designated as "chronic passive congestion of the lungs" is anything but passive if our theory is correct. There are some practical deductions which may be drawn from these considerations which have been brought to the fore by the aid of new instrumentation applied to the catherization of the heart by Cournand and the revival of the ballistocardiograph by Starr.

First, we must consider the network of capillaries spread out in the walls of the alveoli of the lungs. Estimates of the surface covered range from 90 to 140 sq. m. for the aggregate of 725 million alveoli. These capillaries are thought to contain 9 per cent of the blood volume at full inspiration and 6 per cent at the end of expiration. They mark the boundary of the afferent and efferent parts of the heart. As a rule we lose sight of a very important fact about these capillaries, namely, that they receive blood from both ventricles, from the right through the pulmonary artery and from the left through the bronchial artery.

The systolic pressure in the pulmonary artery is relatively low, only 18 to 30 mm. Hg at rest, while that in the bronchial artery is much higher since it comes off the first portion of the aorta. If one pulmonary artery is ligated,[1] blood will fill these capillaries from the dilated bronchial artery and, because of the higher pressure, will distend them greatly, a fact of great clinical importance in connection with embolism of the lungs. If, on the other hand, we were to ligate the bronchial arteries, we would destroy the lungs because the bronchial is the nutrient artery of both the lung and the pulmonary artery which receives its vasa vasorum from it.

The pressure within this capillary network is the resultant of the pressure of the air in the alveoli, the pressure in the two sets of arterioles and the pressure in the pulmonary veins. The capillaries are covered by an exceedingly thin epithelial membrane which is demonstrated with difficulty in the normal lung.[2] The lymphatic vessels of the lung do not reach into the alveolar wall.[3]

We have examined sections of the lungs of guinea pigs which had been killed in a chamber at the pressure of half an atmos-

* From the Department of Medicine of the University of Rochester, School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y.

phere, equivalent to an altitude of 16,400 feet. Great engorgement of the capillaries of the alveolar walls was noted, with thickening and encroachment upon the alveolar spaces. The appearance of these lungs differs in no way from that of a lung in congestive failure of the circulation. It differs in no way from the appearance of the left lung of an animal after Schlaepfer[1] had ligated the left pulmonary artery. In 1934 when the aforementioned observation was made by Hurtado, Kaltreider and McCann[4] we did not know that low oxygen tensions would cause vasoconstriction in the pulmonary arterioles so that we did not then appreciate the reason why the appearance of the lung of the guinea pig at high altitude was identical with that of a dog after ligation of a pulmonary artery and with the lung of a man with congestive failure. It is now the writer's belief that the congestion has the same mechanism in each instance, namely, diminished inflow from the pulmonary artery and increased inflow from the bronchial artery. This view is supported by observations of Motley, in Cournand's laboratory,[5] who observed that inhalation of 10 per cent oxygen in normal man immediately increases the pressure in the pulmonary artery with a decrease in the cardiac output which may amount to as much as 20 per cent. This can be interpreted as a vasoconstrictive effect of low oxygen tensions which von Euler and Liljestrand[6] have demonstrated in cats and which they have attributed to a local action on the arterioles and precapillaries of the lung. These latter workers also found that the effect of low oxygen tensions was to dilate the systemic arterioles as well as to constrict the pulmonary so that we have an additional reason for belief that the congestion seen in the lung of the guinea pig is due to a greater inflow from the bronchial artery coincident with a diminished flow through the pulmonary artery. This is the basis for our belief that the changes in the lung in congestive failure are not passive and that they may depend almost entirely upon anoxia rather than upon back pressure from the left auricle.

A recent report by Lewis and Haymaker[7] records the autopsy findings in seventy-five cases in which death had occurred in flying personnel at altitudes of 17,000 to 31,000 feet as a result of sudden interruption of oxygen supply. All were members of heavy bomber crews who had previously been in excellent health. The lungs were found to be engorged with blood as in the case of our guinea pigs. The veins were congested and edema and hemorrhages were noted in the viscera.

In his classic paper on regulation of the supply of venous blood to the right heart Krogh[8] makes mention of the experiments of Weber who found evidence of an active state of contraction in the pulmonary arterioles which could alter the work of the right heart independently of the left. Krogh dismissed the idea because he could not believe that the work of the right heart could vary independently of the left and also because he believed that the pressure variations in the pulmonary artery were too small to be relied upon. He said, however, "the evidence—is, in my opinion, rather unfavorable to pulmonary vasomotors, but I wish to emphasize that the question is still an open one."

Two patients have recently come under the author's observation who suffered from syncope from severe coughing. One of them had suffered from repeated embolization of the lungs during postoperative thrombophlebitis, hence he was not thought suitable for catheterization of the heart. In the other the attacks occurred during coughing paroxysms induced by smoking. We were able to make the observations shown here in the chest laboratory of our clinic where such studies are being carried out. (Fig. 1.)

Three sets of simultaneous pressure records are shown. The upper strip records the ballistocardiogram (BCG), chest pneumogram (PNG), radial arterial pressure (ART) and right ventricular pressure (VENT) before, during and after a series of coughs of increasing vigor and intensity. The scales

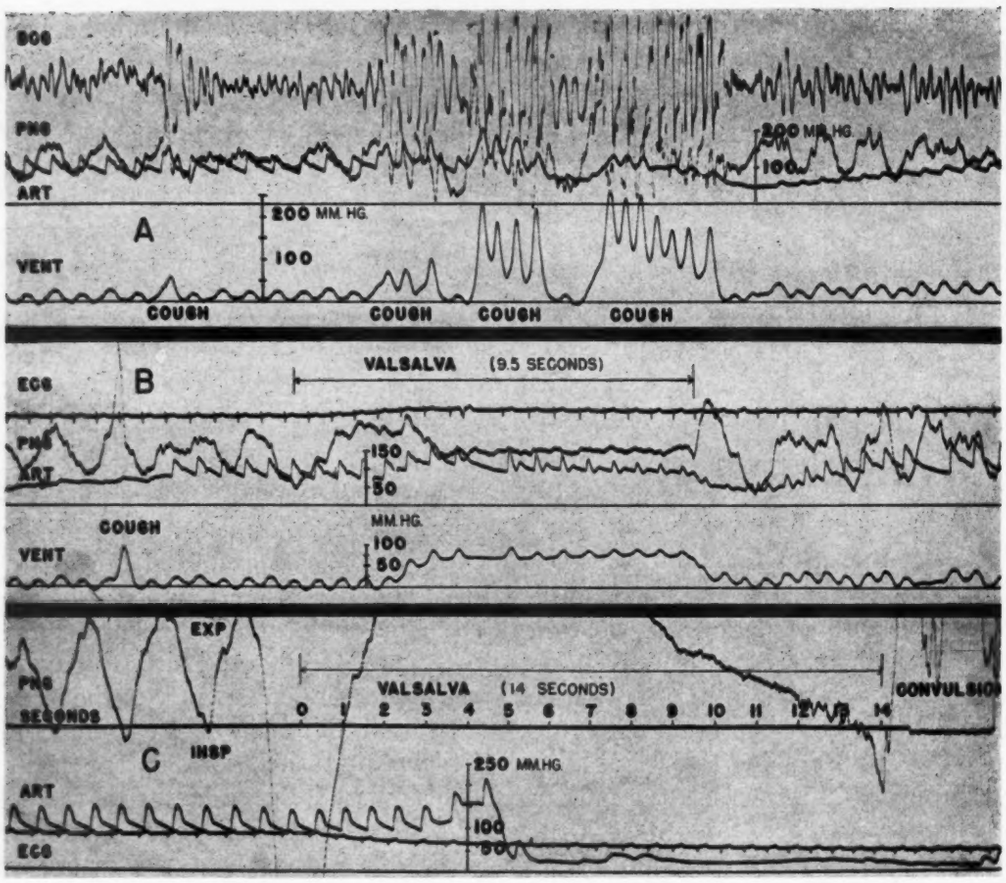

FIG. 1. Graphic records of right ventricular and arterial pressures during coughing and expiration against a closed glottis in a patient with tussive syncope.[30]

indicate pressure changes in mm. Hg. One may note the extraordinary increments in right ventricular and intrathoracic pressures during coughing, rising as high as 250 mm. Hg.

The middle strip records a Valsalva test of short duration. The right ventricular and radial arterial pressures and the electrocardiogram are shown. Note the right ventricular pressure rose to 70 to 85 mm. Hg. The arterial pressure rose at first and then fell to about 50 mm. Hg. Complete syncope did not occur but the patient was dazed and confused.

The lower strip shows the effects of a prolonged Valsalva test. At the beginning of expiration the arterial pressure rose for five beats and then fell sharply to less than 50 mm. Hg with imperceptible pulsations. The patient lost consciousness and after 14 seconds had convulsions.

The full meaning of these observations cannot be stated at this time. It is clear, however, that changes took place in the lung which markedly altered the work of the two ventricles by blocking the passage of blood from the right ventricle to the left, reducing the output of the left ventricle to imperceptible levels, causing syncope followed by convulsions. During the violent expiratory movements of cough and the prolonged expiration against a closed glottis in the Valsalva test the intrathoracic pressure and the right ventricular pressure rose to surprising heights. We were inclined at first to assume that the entire effect was produced by the rise in intra-alveolar pressure, thus blocking the transfer of blood from the right ventricle to the left in a manner similar to that observed by Otis et al.[9] in subjects breathing air under increased pressure, in whom they found increased heart rate and decreased stroke volume and cardiac out-

put. This could have been brought about by blocking entry of blood into the chest.

In our case we believed that there was the additional probability that pulmonary vasospasm may have contributed to the result of raising the pressure in the right ventricle. Consequently the experiment on our subject was repeated at a later date with a bronchoscope in place to maintain a free airway, excluding closure of the glottis during any phase of the coughing effort. In this last experiment the same extraordinary rise in right ventricular pressure was observed although the airway was free. A catheter for recording intratracheal air pressure was introduced and the bronchoscope withdrawn. A marked rise in intratracheal pressure was observed but this pressure was lower than the right ventricular pressure. Even though the airway was maintained by the bronchoscope there still is the possibility that bronchospasm as well as vasospasm occurred. We cannot at this point consider these two factors separately. It may never be possible to do so. The experiment will be resumed after an interval in which the trauma has had time to heal. Without going further we have seen a striking example of the way in which the lung may operate as a check-valve.

The case referred to in the aforementioned experiment is undoubtedly an example of a condition originally described by Charcot in 1876 and which has subsequently come to be called "laryngeal epilepsy." Recent descriptions of the condition have been made by Whitty[10] and Rook.[11] Our patient has some peculiarity in his manner of coughing which makes him differ from the usual normal subjects such as have been studied by Lauson, Bloomfield and Cournand,[13] who did not observe such striking elevations of right ventricular pressure during coughing or the Valsalva experiment.

Let us consider the possible effects of a sharp violent expiration throwing a considerable volume of abdominal venous blood into the right atrium. It would seem that the crest of this venous flood would have devastating effects upon the alveolar capillaries unless some mechanism were operating to protect them from rupture. This protection against such mechanical injury of the alveolar capillaries could conceivably be accomplished in two ways: one by bronchial constriction raising the alveolar air pressure, also by pulmonary arteriolar constriction, also the tonus of the right ventricle or all acting together to serve as a cushion for such a water hammer blow to the alveolar wall. Teleologic reasoning is dangerous and we must avoid it. We can, however, obtain some indirect support for the idea from several sources. From the laboratory of Stead[12] are some observations of the effects of rapid injection of 1 L. of 5 per cent albumin solutions on right ventricular pressure and cardiac output of normal subjects. Such an injection increased the blood volume and raised the right atrial pressure yet there was no consistent effect upon cardiac output such as one would postulate from Starling's law of the heart. When, however, Stead's data are examined, one finds that cardiac output was increased in one-half his subjects by an average amount of 32 per cent and that it was maintained to the end of an hour. In some of the remaining cases it fell or underwent no change. In those cases in which the cardiac output increased it did not do so in proportion to the rise in right auricular pressure. There are indications, therefore, that certain mechanisms operated to cushion the effect of such a sudden increase in blood volume, venous return and atrial pressure. Increased tonus of bronchi or of pulmonary arterioles or both may have occurred. Other factors to be considered are the venopressor tone, the tonus of the right heart and the rate of diuresis.

The more one considers the manner in which the lung may regulate the blood flow the more intriguing the concept becomes. Here we may have the means by which we may resolve some very old riddles and controversies concerning the genesis of con-

gestive failure, regulation of coronary blood flow and apparent discrepancies in Starling's law of the heart.[14]

Prepossession of our interest with the heart itself, or with any single aspect of the circulation, may blind us to the importance of other facts. There is no single aspect of the circulation which we can understand except in its relation to the whole homeostatic mechanism. In thinking of the failure of the circulation we are apt to go round and round the list of functions which it serves: respiration of the cells, their nutrition, distribution of fluids, excretion, volume regulation and heat regulation. Starr[15] asks where the train starts. The answer is that it may start at any station. Thus beri-beri heart disease starts at nutrition; heat prostration starts at thermoregulation, etc. Those who think primarily of the heart itself may battle over the concepts of backward failure, forward failure and ventricular imbalance, but they have to reckon with those who consider blood volume the central factor in states of shock and congestive failure,[16,17] or those who, like Yandell Henderson,[18] regard the venopressor mechanism as of equal importance with the heart itself. We prefer to regard anoxia as the central starting point and divide circulatory failure into two types: one, anoxia with acapnia; the other, anoxia with hypercapnia.

Let us now construct a theory as to the manner in which the check-valve function of the lung takes part in the genesis of congestive failure of the circulation. We will start with the situations arising from anoxic anoxia. The immediate effects of this are hyperpnea with loss of carbon dioxide. If the lungs are normal, the vital capacity is reduced and the residual air is increased, presumably by bronchoconstriction as we have shown,[4] while at the same time the pulmonary arterioles also contract.[5,6] The result of this action in the lung is to raise the pressure in the right heart and ultimately in the veins. We also assume that congestion of the lungs results from increased bronchial inflow as the pulmonary inflow decreases, an assumption supported by the studies of Wood and Miller.[19]

Meanwhile, anoxia has increased the transudation of water across the capillary walls stimulating the flow of lymph from the thoracic duct until such time as the rising pressure in the veins comes to equilibrium with pressure in the lymph ducts checking the flow. For still undetermined reasons the kidneys diminish the excretion of water and salt, at which point in the sequence of events the stage is set for the steady accumulation of fluids in the tissues, the production of edema and the rise of thoracic duct pressure until it reaches the point at which lymph may again flow into the veins. By this sequence the volume of the blood is built up since flow of blood from the veins to the lymph duct is prevented by valves. Thus we have accounted for the most striking features of congestive failure, namely, cyanosis, dyspnea, edema, elevated venous pressure and increased volume of the blood.

It is to be observed that so far we have used the term "congestive failure of the circulation" without mention of the heart itself. The situation just described would apply to the development of congestive failure in an individual with a normal heart if he were to go to an altitude beyond the ceiling to which he could adapt his circulation and respiration.[7] It is obvious that the ceiling would be lower if either the myocardium or the lung were impaired by a pathologic process and that the ceiling tolerated would be higher for a resting man than for one at work. The essence of the development of the anoxic anoxia with which we started is the inadequacy of the maximal cardiac output to meet the metabolic demands for oxygen, and this conception would hold true whether the myocardium were normal or pathologic. In practice, however, congestive failure usually occurs in association with heart disease. If some process should diminish the functional capacity of the left ventricle, such as coronary sclerosis, hypertension or lesions of the valves of the left heart, we usually observe the phenomena which we

have described and which we may refer to as left-sided failure.

If the lungs in such instances were to fail to function as a check-valve by broncho- and vasoconstriction, acapnia would result. Anoxia with acapnia would result in shock rather than congestive failure since the venopressor mechanism is dependent upon a normal carbon dioxide tension. Thus the anoxic loss of fluid across capillary walls would not be balanced by an equal return of fluid to the right heart and the circulating blood volume would be diminished. If, on the other hand, the pulmonary check-valve operates, a certain degree of compensatory emphysema is thereby established and the rapid loss of carbon dioxide prevented in whole or in part.

If we examine the data of Peters and Barr,[20] we find that the arterial pCO_2 ranged from 39.7 mm. to 52.2 mm. Hg in patients with cardiac dyspnea. This would indicate that the pulmonary regulation of carbon dioxide was adequate to establish a normal level and that it might at times overcompensate to produce a hypercapnia. The fact that Peters and Barr[20] found in some instances a low CO_2 absorption curve might indicate a preliminary period in which there had been hypocapnia partly compensated by the renal excretion of extra fixed base or, as an alternative explanation, by accumulation of lactic acid. The data in their paper are not adequate to establish this point.

If, on the other hand, the primary pathologic process were in the lungs, the anoxia might be primarily of pulmonary origin, as in emphysema and fibrosis, embolism of the lungs or in primary pulmonary hypertension but with the additional factor of strain upon the right ventricle. When congestive failure occurs under these circumstances, it differs from the first type described in that the carbon dioxide tension of the blood is usually high; and we may speak of anoxia with hypercapnia as corresponding generally with what is sometimes called right heart failure or cor pulmonale.

There are several special situations which fit into this scheme of things: for instance, circulatory failure in pneumonia which is rarely congestive and in which anoxia and acapnia exist. The difference in this instance is due to the failure of the venopressor mechanisms and diminished blood volume leading to shock rather than congestion.

Starling[14] stated his law of the heart as follows: "The energy set free at each contraction of the heart is a simple function of the length of fibres composing its muscular walls." According to this law the demands for an increase in blood flow are met by an increase in diastolic volume which permits a greater ejection of blood. In general one would expect that the effect of an increase in venous or right atrial pressure would result in a greater cardiac output and this appears to be true of the normal heart within limits. When these limits are exceeded, a further rise in right atrial pressure may be associated with a falling-off of output. The more the heart muscle is weakened by a pathologic process the greater must be the diastolic volume required to effect a given level of output, and the higher will be the venous pressure required to reach its peak output which, because of the weakened muscle, will be below that of a normal heart. It is consistent with this law that Burwell[21] found a lower venous pressure and a lower cardiac output when digitalis was given to men with normal hearts. In contrast to this the action of digitalis in congestive failure is such that it lowers the right atrial pressure in the failing heart and usually causes an increase in cardiac output.[22,23] The same thing generally applies to any agency which accomplishes a lowering of the venous pressure in failure of the congestive type. McMichael and Sharpey-Schafer[24] have given an excellent illustration of this by showing that the reduction in venous pressure merely enables an overdilated heart to approach the optimal level of dilatation at which its output is greater. Venous stasis by use of cuffs, venesection or diuresis will frequently bring about this desired result. Administration of oxygen would have favor-

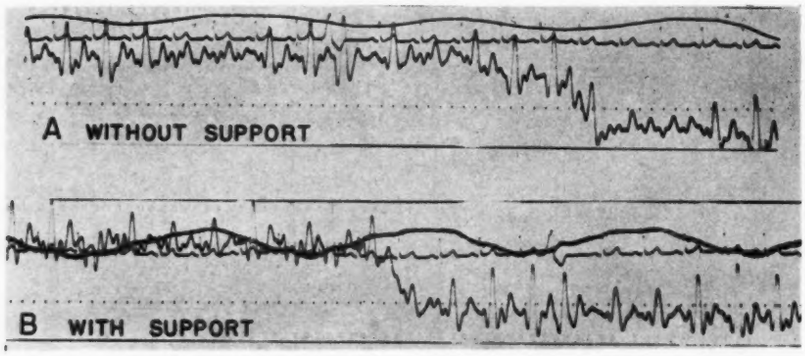

FIG. 2. A typical record of a man of fifty with angina pectoris of two years' duration, blood pressure 130/75, with a normal electrocardiogram, is presented in tracing A. No other objective signs of heart disease were present. Note the increased respiratory variation with very small complexes present during expiration. Tracing B demonstrates the marked improvement in definitiveness and increase in the amplitude of the complexes during expiration following the application of a rigid abdominal support. Not only did this man's pattern improve but he has been wearing the support for over two months now and has been free from anginal symptoms. The upward deflection of the pneumograph record is expiratory.

able effects in a variety of ways, not the least of which would be that of relieving the vasospasm and the bronchial constriction in the pulmonary check-valve. Similarly one might expect benefit from vaso- and bronchodilator drugs.

Data may be taken from a paper by Howarth, McMichael and Sharpey-Schafer[25] to illustrate the actions of aminophylline. One may note that reduction in right atrial pressure by application of a cuff on the extremities was not accompanied by an increase in output such as sometimes occurs. When the cuff was released, the atrial pressure rose again, at which point injection of aminophylline was followed by a prompt fall in right atrial pressure and as prompt a rise in cardiac output. I should like to point out that this whole effect could have been brought about through the action of the drug on the check-valve since it is a known bronchodilator and vasodilator. It may have had a direct stimulating effect upon the myocardium, as these authors suggest, but in the writer's opinion the pulmonary action offers an explanation equally good.

From the foregoing I hope that I have made clear the manner in which the pulmonary check-valve makes it necessary to consider the application of Starling's law to each ventricle separately and how the conception of the check-valve enables us to resolve the apparent discrepancy between the relations of venous pressure and cardiac output in the normal heart and in the failing heart.

As a coronary dilator aminophylline is disappointing and it is hard to see how such action could occur in many of the extremely sclerotic coronaries which we find at autopsy. Yet aminophylline may increase coronary flow even in these sclerosed vessels simply by increasing the cardiac output and lowering the pressure at the venous end of the coronary system. This brings us to a consideration of the way in which the check-valve may play a part in the production of angina pectoris.

In our own laboratories Brown and Hoffman[26] have observed respiratory variations in many ballistocardiograms, as have Starr[15] and others. Even in normal individuals the amplitude of the waves is decreased at peak expiration and increased at peak inspiration Such findings are quite consistent with the findings of Lauson, Bloomfield and Cournand,[13] using the cardiac catheter to measure the respiratory variations in pulmonary blood flow. From their data we may see that as the intrathoracic pressure falls in inspiration the amount of blood in the lungs increases, the right ventricular

stroke volume is greater and the left ventricular stroke volume becomes less. In expiration the reverse occurs.

The studies of Brown[26] show that there are four groups of patients in which larger than normal respiratory variations are observed: those having angina pectoris, emphysema and fibrosis of the lungs, hypertension, and those who have had thoracolumbar sympathectomy. Their studies show that the expiratory output of the heart is more impaired than the inspiratory. They have also observed the respiratory variation in patients before and after a Smithwick sympathectomy. After operation it was greatly increased and great improvement followed the use of abdominal support.

Figure 2 shows the ballistocardiogram and electrocardiogram of a patient with angina pectoris. He was a man of fifty, with angina of two years' duration. Blood pressure and electrocardiogram were normal yet the ballistocardiogram showed an abnormally large respiratory variation which was relieved by use of abdominal support as Kerr found to be the case in many instances.[27] Unfortunately use of a belt frequently fails to relieve such patients and may even increase their difficulty. Such instances are usually those in which there is a great deal of emphysema, varicose veins or both. This is obviously a field for further study. Perhaps the matter is one of finding the optimal pressure to be applied to the abdomen which will facilitate the transfer of blood from belly to chest without at the same time impeding the entrance of blood from the legs.

Emphysema is one of the most common defects of middle life and old age. It is so common that we frequently take it for granted and neglect to consider its great importance in limiting working capacity. We shall take a moment to consider it in relation to the pulmonary blood flow and operation of the check-valve. At an autopsy of patients with emphysema Parker[28] found that 75 per cent had increased thickness of the right ventricle, 66 per cent had sclerosis of the arterioles and 80 per cent had sclerosis of the larger pulmonary arteries. Kaump[29] reports finding, in the lungs of patients with emphysema, changes in the arterioles resembling those found in similar vessels in systemic hypertension, and he has also found them in a case in which there was no emphysema or fibrosis which he regarded as an instance of primary pulmonary hypertention. When these emphysematous changes are pronounced, it is easy to see why coronary blood flow might be impaired and why application of pressure to the abdomen might fail to improve it, especially if this procedure were to raise the pressure in the right atrium and in the coronary sinus without improving the cardiac output.

I hope that it has been made clear that the lung plays more than a passive role in regulation of the circulation. There is no aspect of the circulation which we can afford to neglect and no aspect that we can afford to emphasize at the expanse of others. If that seems to have been done here, it was only for the purpose of pointing out our neglect of this function of the lungs and in the hope that the conception of the check-valve may be like finding the light switch in the darkened room, one which will enable us to put the facts of the circulation together in orderly fashion. We have seen how this conception enables us to understand how vaso- and bronchoconstriction in the lung may modify the transfer of blood from right ventricle to left and how it may play a crucial role in the genesis of congestive failure. In the light of this conception we must interpret Starling's law as applying to each ventricle separately. The exaggerated respiratory variation in the ballistocardiogram which is regularly observed in patients with angina pectoris may depend upon abnormal resistance within the lung as well as upon other factors which impair the mechanical effects of breathing on the venous return. Further study of this neglected aspect of cardiology may throw much light on the genesis of angina pectoris and on the prevention of coronary thrombosis.

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Seminars on Cancer Research

An Introduction to Cancer Research*

G. Burroughs Mider, M.D.

Rochester, New York

Cancer research in the United States is carried out both in medical schools and independent research institutes. Almost every scientific discipline contributes something to our knowledge of growth. The cooperative effort of scientists trained in orthodox disciplines seems the most effective way of prosecuting cancer research. The day of the individual investigator is by no means past for his ideas are of paramount importance in the solution of problems.

The majority of investigators derive their financial support from extramural sources. Grants for one to three years are made on the basis of specific projects outlined in detail by principal investigators after the applications have been screened by committees of outstanding scientific workers. Some support is available at this time for the development of new technics and new approaches but project research connotes that sufficient data are available to show that the idea is not only sound but that its solution is practical.

Prior to the passage of the National Cancer Institute Act the majority of cancer research was done on a small scale supported principally from university budgets and from small grants-in-aid provided by those philanthropic foundations interested in cancer problems. Today the bulk of the work derives its financial support from public funds either obtained by direct solicitation or from tax monies. The public trust imposed on those who process grants is fully recognized as a great responsibility. It has been discharged most capably.

The advent of public monies into the field has been followed by withdrawal of the interest of at least one prominent foundation from which support was previously obtained. The general public seems to believe that the major part of the funds expended on cancer is for fundamental research, but only 25 to 30 per cent of all money allocated in the general field of cancer is used directly for clinical or laboratory investigation. The expenditure of approximately $7,000,000 in the last year for cancer research may be justified readily from the progress made in obtaining facts pertinent to fundamental aspects of cancer which may be just as important in elucidating problems regarding non-neoplastic growth processes. The future of cancer research and therefore the control of cancer depends on continued support of the public, both lay and medical. As larger segments of the population are included among the age groups in which cancer commonly occurs (Fig. 1), the magnitude of the medical, social and economic problems raised by neoplastic diseases will increase. No one can foresee how much more time and effort must be expended before practical methods for adequate control of common forms of cancer may be available.

Physicians may find it difficult to reconcile the optimism of the public press with their personal experience in treating an ever increasing proportion of cancer patients. Nevertheless much information regarding fundamental aspects of cancer has accumulated. Many more facts must be acquired before the knowledge essential to completely effective control of neoplastic diseases will be available. This paper will

* From the Division of Cancer Research, Department of Surgery, the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

serve as an introduction to more detailed consideration of carcinogenic agents, carcinogenesis, genetic and viral aspects of cancer and cancer chemotherapy. The material included pertains directly to neoplasia, is not treated exhaustively and might be interpreted differently by others. Many important contributions have been omitted since some of them have been discussed extensively in a recent review by Rhoads[107] or in Greenstein's excellent monograph.[46]

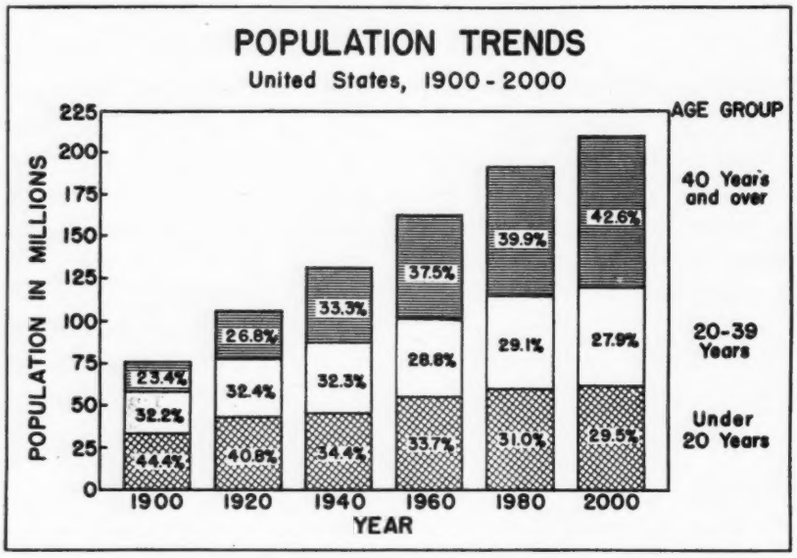

FIG. 1. Population trends in United States.

Long ago the basic fact that cancer results from the interaction of environment and heredity was deduced from clinical observation by Sir James Earle, commenting on soot cancer described by Percival Pott.[104] A wealth of clinical and experimental data acquired subsequently has done little to change this concept of the etiology of cancer. Further study of occupational cancers has continued to afford evidence that different substances may be capable of producing cancer under circumstances which include a latent period of years intervening between exposure to the inciting agent and its effect.[40,49,57,58] Most of the well authenticated studies have been made by European investigators but Machle and Gregorius[80] have reported recently an unusually high incidence of pulmonary cancer among chromate workers in the United States. Circumstantial evidence plays an important role[127] in evaluation of the relation between industrial hazards and cancer which the laboratory is most helpful in elucidating. Not all workers exposed to a carcinogenic industrial hazard develop malignant neoplasms nor is the total number of patients afflicted with occupational cancer a numerically significant proportion of the cancerous population. Their importance lies in the support they lend in applying data obtained from animal experiments to the human problem.

Investigators sought to isolate one or more chemicals from coal tar which would produce skin cancer in experimental animals. The research culminated in the isolation of 3,4-benzpyrene in 1933[20] after 1,2,5,6-dibenzanthracene had been found to be the first chemical compound manifesting pronounced carcinogenic properties under laboratory conditions.[64] The list of carcinogenic cyclopentenophenanthrene hydrocarbons grew rapidly through the efforts of Kennaway, Cook and Hieger in London and Fieser, Shear and Andervont in Boston. Interest in the structural similarity of these compounds to some naturally occurring hormones was increased by Lacassagne's observation[72] that castrated male mice developed mammary cancer after estro-

genization though spontaneous tumors of the breast occurred solely in female mice. Any hope that a specific chemical configuration might be essential to cancerigenesis was soon dispelled for several hundred agents including many aliphatic and aromatic compounds and some inorganic chemicals were found to have carcinogenic properties.

The responses elicited in rodents by different types of carcinogenic chemicals vary. The synthetic hydrocarbons, for example, may evoke neoplasms in tissues of mice with which they come in contact. They are less effective in producing tumors in rats and still less potent in guinea pigs and rabbits. Percutaneous administration increases the incidence of some cancerous and related diseases to which some strains of mice are spontaneously susceptible, causing these lesions to appear at an earlier age than usual. The carcinogenic azo dyes produce primary hepatic neoplasms when fed to rats but rarely elicit tumors at the site of implantation in this species.[78] Some of them, however, may produce neoplasms both at the site of contact or at a distance when injected into mice. A wide variety of carcinomas as well as leukemias and sarcomas may follow the feeding of 2-acetamino-fluorene to rats but this agent is less carcinogenic for mice. Ethyl carbamate (urethane) seems to be effective only in producing pulmonary neoplasms. Chloroform and carbon tetrachloride evoke only hepatomas.

The effective dose of a carcinogen for mice may be incredibly small. Increasingly large doses increase tumor incidence and decrease the time required for their production until a maximum yield of neoplasms, frequently approaching 100 per cent, is evoked in a minimum period of time, usually three to four months. Large dosages may reduce tumor incidence by increasing the mortality from toxic side effects. Slight changes in a carcinogenic molecule may enhance, reduce or abolish its ability to provoke cancer. Chemical agents not carcinogenic in themselves may accelerate or retard tumor formation by cancerigenic agents. Simple caloric restriction, deprivation of dietary sulfur-containing amino acids, increasing the consumption of fats or riboflavin may affect the number of tumors produced by a standard technic.

Not all carcinogenic agents are products of chemical synthesis. Schabad[112] was the first to produce neoplasms in lower animals from an extract of human liver. His observation has been amply confirmed. Carcinogenic activity has been found in an unsaponifiable fraction extracted from various organs and tissues.[54,126] Hieger found that the carcinogenecity of the extracts seemed to be associated with a cholesterol-rich fraction. Cholesterol itself, though not carcinogenic in small scale experiments, nevertheless does possess definite though slight carcinogenic activity even when highly purified.[53,54] Greenstein[46] has pointed out that the extraction procedures may be sufficiently drastic to alter an innocuous, naturally occurring substance and produce a carcinogen, for pyrolysis products of cholesterol are capable of producing tumors in mice.[63] Furthermore, Beck and Peacock have succeeded in inducing subcutaneous[8] and gastric tumors[97] in mice with ordinary cottonseed oil that has been heated to 360°C. for one hour—a temperature that may be reached in cooking. Cholesterol exposed to the same degree of heat yields substances that are intermediates in the transformation of cholesterol to methylcholanthrene but results of their bioassay for carcinogenic potency have not yet been reported.[29]

Another class of chemicals incriminated in cancer production are estrogenic substances whether or not they occur in nature or are synthetic chemicals with estrogenic activity. Mammary carcinoma can be abolished in stocks of mice susceptible to it if they are oophorectomized at the proper age. Murray[93] was able to induce cancers of the breast in castrated female mice by implantation of ovarian tissue and, as stated above, Lacassagne[72] showed that estrogen was responsible for these phe-

nomena. Female mice of some strains from which ovaries were removed shortly after birth developed mammary cancers though in reduced incidence.[30] This is due, presumably, to an effort by adrenal glands to compensate in some measure for the absence of the gonads[31] since the changes observed in some tissues of gonadectomized mice of both sexes are similar to those ininduced by estrogens.[37,138] Androgens may nullify the effect of estrogen on the breast tumor incidence. Evidence that estrogenic hormones are carcinogenic for the human breast and uterus continues to be presented in the literature from time to time. The thesis has been reviewed recently by Zondek.[140] It may be argued that the female sex hormone is essential to the anatomic integrity of mammary tissue and that its hyperdevelopment and preservation beyond the natural sex life of the individual is solely responsible for the apparent carcinogenecity of estrogens. However, estrogenization of suitable mice also leads to the production of hypophyseal chromophobe adenomas, interstitial cell tumors of the testes, lymphomas and carcinomas of the uterine cervix. Estrogens have been implicated in the origin of spontaneous mammary neoplasms in rabbits.[17,42] It is difficult to evaluate the specific role that estrogens play in the induction of these lesions. The dose required to effect tumor production exceeds physiologic levels. Certainly the usual hormonal interreactions involving the reproductive organs are disturbed. Imbalance of sex hormones produced by other means may also evoke tumors. Some castrated mice develop adrenal cortical hyperplasia which, in certain strains, eventually leads to adrenal carcinoma.[30,31,37] Tumorigenesis under these conditions can be averted by estrogenization[139] but the cancers themselves may produce sex hormones.[34] Transplantation of ovarian tissue to the spleens of castrated mice results in the formation of granulosa cell tumors or thecomas in the grafts.[10] Excellent discussions of the endocrine imbalances involved in the pathogenesis of these tumors are available.[39,75,76]

Not all carcinogenic agents are chemicals. The high incidence of skin cancer on body surfaces exposed to sunlight among outdoor workers, particularly sailors and farmers, led to experimental investigation of the cancer-producing properties of ultraviolet light. Extensive studies indicate that tumors of the skin of rats or mice may be induced by ultraviolet irradiation of approximately the same wave lengths that cause sunburn of human skin. A single dose of carcinogenic ultraviolet rays did not produce cancer. Blum has recently correlated the data obtained from the laboratory and clinic.[15]

The tragic consequences to man of excessive exposure to roentgen rays or radioactive emanations are too well known to require amplification with respect to skin and bone cancer. The untoward incidence of leukemia and related diseases among roentgenologists[81] is reflected in the potent leukemogenic properties of energizing rays in mice[50] even though the strain be not particularly susceptible to the occurrence of spontaneous leukemias or to its induction by chemical agents.[83] Furth[35] has studied the granulosa cell and related tumors that follow total body irradiation in mice. It seems to make little difference whether the effective dose of irradiation be delivered from an x-ray tube, radium, mesothorium or radioactive isotopes. The results have been identical whenever tested.[9,21,73,79,96,110,116,117,125]

There are many other carcinogens. Some viruses are known to be carcinogenic for some species and, in general, produce their effects more rapidly than do other carcinogenic agents. Beryllium salts may produce osteogenic sarcoma in rabbits.[36] Epidermoid carcinoma may develop in burn scars.[131] Certain nitrogen mustards may cause tumors in mice.[16] The agent responsible for the transition, normal to cancerous, is not essential to the perpetuation of the new race once it has been produced. To what extent the agents that effect malignant neoplasms are capable of eliciting cancer in

man is conjectural but scientists are well aware of the problem. Fieser,[32] referring to hydrocarbon carcinogenesis, said: "I know of no instance of any authentic isolation of a carcinogen associated with spontaneous cancer. . . . I feel that the question is still

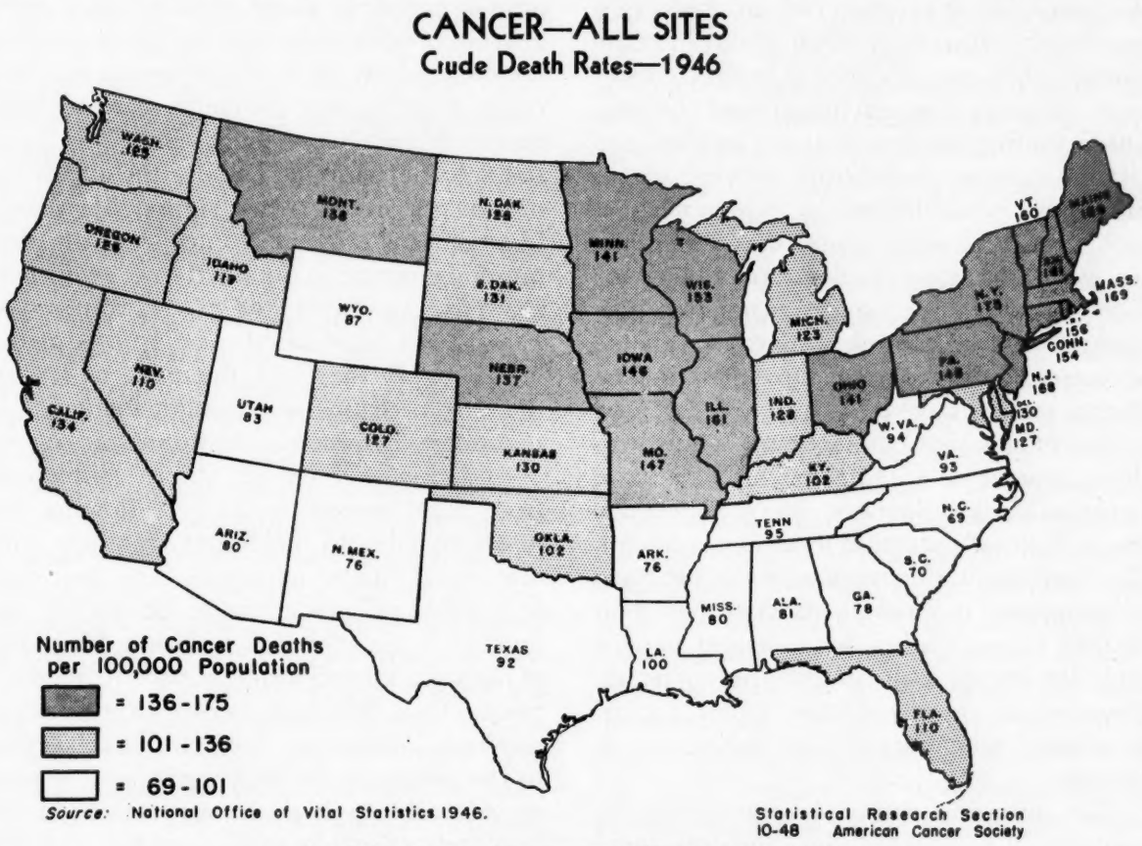

FIG. 2. Death rates from cancer in United States, 1946.

open. . . . Is there any unequivocal evidence that any one of these compounds is capable of producing cancer in humans? The nearest that one can come to establishing a case is to cite the facts that certain coal tars very probably have produced skin cancer in workmen in certain industrial plants and that Cook and Hewett isolated benzpyrene from certain coal tars that were carcinogenic to mice. However plausible it may appear that benzpyrene has been responsible for instances of human skin cancer, direct evidence is lacking. . . . "

Salter[111] wrote more recently: "Despite a wealth of data indicating carcinogenesis in man from crude mixtures, only three unadulterated agents have thus far been proved carcinogenic for man. These are (1) radiation, (2) betanaphthylamine and (3) arsenic. Chemical compounds which are outstanding carcinogens in rodents have usually proved ineffective in other species and have not been shown effective in man. Therefore, carcinogenic activity in rodents should not be used as a criterion of possible danger to man; nor should its absence in rodents be regarded as valid evidence of safety for human workers. . . ."

Correlation of data obtained from laboratory study of carcinogenesis and clinical data may be effected through greater emphasis on the epidemiology of cancer in man. The mortality rate from specific anatomic types of cancer is not only different among the various nations of the world but even among the forty-eight states of this country.[19] (Fig. 2.) The autopsy incidence of primary cancer of the liver in the South African Bantu is 45 per cent. In the West African Negro hepatic neoplasms account

for 18.7 per cent of cancer deaths. Studies reported from the Cook County Hospital, Chicago, indicate that there is no difference in the autopsy incidence of cancer of the liver among whites and negroes, and that the proportion 1.1 per cent in Chicago is the same as that observed in European countries.[61] Certainly such data indicate strongly that the incidence of hepatic cancer must depend on environmental factors. Other findings suggest that the incidence of clinical cancers of the lung, larynx, uterus and penis is influenced by non-genic factors.[65,66,67,115] Levin[77] urges that systematic study in the epidemiology of cancer be incorporated in the rapidly expanding program of cancer research. Programs directed at elucidating the role of environment in producing cancer have been initiated recently.

The effects that carcinogenic agents produce depend to a large extent on certain constitutional influences which determine the individual's reaction to an environment. The high familial incidence of specific types of neoplastic diseases in rodents and their further concentration by accepted genetic technics leaves little doubt that gene influences are an important factor in determining susceptibility or resistance to cancer.

The situation today is extraordinarily complex for susceptibility and resistance are purely relative terms. It is pertinent to recall that genes and characters are not synonymous. The character is an effect, in this case a neoplasm. The gene is an inheritable factor, the tumor is not.[51] The use of heterogeneous stocks of mice has been replaced by the use of inbred strains obtained and continued by brother-sister mating, thus eventually achieving a high degree of homozygosity. Individuals from a given strain are almost as closely related as are human monovular twins. Their tumor incidence is predictable within narrow limits under standardized conditions and experimental procedures designed to influence it give highly reproducible results.

A combination of genic and environmental influences will determine whether or not cancer will be manifest. This may be illustrated by a brief summary of the factors known to be involved in the production of mammary cancer in mice.[92]

Little and his associates[123,124] found that the incidence of breast tumors was higher among progeny whose mothers were from a strain of mice with high mammary cancer incidence than when the maternal ancestor came from a low incidence strain. Had simple Mendelian genetic principles been the sole determining factor, the incidence of cancers of the breast should have been identical in progeny comprising the first familial generation obtained from reciprocal matings. An important extrachromosomal factor was postulated and subsequently found by Bittner[11] in the milk of female mice from strains with a high incidence of mammary carcinoma. Spontaneous tumors of the breast could be almost eliminated from high cancer stocks by allowing the newborn mice to suckle only mothers with low breast cancer pedigrees. The incidence of mammary cancer could be greatly increased in some strains with low incidence of mammary carcinoma by permitting their young to suckle high breast cancer strain mothers. When mice from strains refractory to the action of the milk agent were mated reciprocally to high breast cancer stocks and their offspring were provided with the milk factor, the incidence of mammary tumors in the first filial generations was similar. This indicated that susceptibility to the action of the milk agent was determined to a large extent by genetic factors. The precise physiologic mechanisms that are controlled by gene action are the subject of intense investigation.[12,22,52,71]

Perhaps the milk agent is not essential to the production of mammary cancer in mice. Bittner has consistently reported the occurrence of a few tumors arising in the breasts of mice foster-nursed by low breast cancer strain mothers. Kirschbaum, Williams and Bittner[70] were able to induce mammary carcinomas in mice in the absence or presence of the milk agent by the percutaneous administration of 20-methyl-

cholanthrene. Heston[52] has reported a breast cancer incidence of 24 per cent among females of a highly susceptible strain delivered by hysterotomy and nursed by mothers of an extremely low breast cancer strain.

No evidence has yet been presented that a factor is present in the milk of any other species than the mouse which might influence the incidence of mammary cancer. That the incidence of clinical carcinoma of the breast may be significantly reduced by preventing breast nursing of infants[48] represents a flagrant extrapolation of data wholly unjustified by our current knowledge.

Genetic influences are important in the production of pulmonary tumors and leukemias in mice, in mammary and uterine tumors of rabbits and indeed in some cancers that affect man.

Relatively few human family histories have been published in which the incidence of one or two types of cancer remain high in successive generations as it does in mice. Most physicians, however, can cite examples of an extraordinarily high incidence of various types of malignant neoplasms affecting one or two generations of the same family, in some cases eradicating the family altogether. Recently published studies from England[98,121] and from Denmark[62] indicate a higher death rate from and frequency of mammary cancer in families of patients with that disease but no higher death rate from or incidence of other forms of cancer than would be expected in the general population.

More data on the familial occurrence of cancer in humans are needed. It seems improbable that the conventional historical approach can elucidate this aspect of the cancer problem effectively. A well planned forward looking technic should offer a better opportunity for acquiring the necessary data, particularly if it be correlated closely with the public health activities of those states in which cancer is reportable by law. The additional cost should be relatively small and the interest of government seems essential to assure continuity of a program that probably cannot be accomplished in one lifetime. The greatest hazard attends the application of genetic data from mouse to man, for each of these highly inbred strains probably represents but one individual in human terms. Perhaps the same principles that govern carcinogenesis in them apply to *some* human beings but with so much variation in response from strain to strain one would expect that even more permutations and combinations might be found in the vast hybrid population that characterizes man.

The nature of the fundamental change involved in cancer production has provoked much speculation on the basis of known facts regarding normal and abnormal growth. Exponents of the virus theory of cancer hold that viral infection is responsible for its origin as indeed it is in some few isolated examples in mammals. The extremists, however, hold that all malignant neoplasms may be of virus origin though the *agents provocateurs* have yet to be isolated and identified. Bodies of the same dimensions as Rous sarcoma virus as determined from *in vitro* studies of the potent agent have been demonstrated by electron microscopy in close relationship to tumor cells known to have been produced by its action.[18] Bodies, presumably the milk agent of mouse mammary carcinoma, can also be demonstrated by the electron microscope.[103] One group has isolated characteristic virus-like particles from the milk of a strain of mice in which mammary carcinoma occurs frequently. This substance produces the characteristic disease when injected intraperitoneally into mice from a strain in which the spontaneous incidence of breast tumors is extremely low.[41] Other intracytoplasmic bodies of unknown nature, revealed by the electron microscope, seem to occur in greater concentration in neoplastic than in normal rat cells but are present in both.[102] There is no evidence that these tumors are associated with viruses. If the bodies be related to carcinogenesis, much of the virus exponents' argument may depend on one's definition of virus. It is not inconceivable that a

normal constituent of cells may attain a predominant role in the cell's metabolism through increase in its concentration to the point where it alters the cell's reaction to its environment.

A thought-provoking discussion of the peculiarities of malignant tumor cells has been presented by Kidd.[68] He has found non-pathogenic immunologically distinctive constituents in cells of certain rabbit neoplasms not known to be caused by viruses. Each tumor studied has its own specific substance. Brown-Pearce tumor cells incubated with sera containing the specific antibody fail to grow on subsequent transplantation. Rabbits which produce specific antibodies after injection of cell-free extracts of the Brown-Pearce tumor prove resistant to the growth of transplanted tumor cells.[69] The role of the distinctive constituents in the autonomy of cancer, their relation to viruses or to formed constituents of cytoplasm, and indeed their presence in the generality of malignant neoplasms remains to be determined. These observations may be interpreted to support the thesis that cancer cells result from the dominance of some substance or substances that intensify growth processes.

Rous[109] has recently stated, "The conclusion that tumor cells are not merely ordinary cells which have seized an opportunity to go on the loose, but differ from them in some distinctive way—a way yet to be ascertained—underlies the present day searching for chemical traits peculiar to cells in the neoplastic state."

Cancer cells, as far as we know, do not differ from their normal counterparts in the chemical quality of their constituents.

Warburg[133] found that an excessively high rate of anaerobic glycolysis and a diminished Pasteur effect characterized the *in vitro* metabolism of cancerous tissues. Indirect evidence indicates that tumors glycolyze *in vivo* as well.

This thesis has been developed further by the characterization of the enzymic pattern of neoplastic cells as compared to their normal tissues of origin. Greenstein,[46] a leading worker in this field, has deduced certain generalizations from this work, amply supported by the experimental data gathered together in his recent monograph. These, briefly stated, are:

"a. Each normal tissue is characterized by the possession of an individual pattern of enzymic activity which may serve to distinguish it from all other tissues.

"b. Tumors have qualitatively the same enzymes as normal tissues. . . .

"c. The enzymatic pattern of a tumor is largely independent of its age, of its growth rate and of the strain of animal in which it is grown. . . .

"d. The range of activity of each enzyme and of concentration of such components as the vitamins is much narrower among tumors than among normal tissues, i.e., tumors possess a more uniform and less diverse chemical pattern than normal tissues. . . .

"e. When a normal tissue becomes neoplastic, many of the specific functional activities markedly decrease or are lost altogether. . . . To a large extent, the diversity of the chemical pattern in normal tissues is due to the presence of certain systems in very high, as well as very low, degree.

"f. The range of values for the tumors is usually between the extremes of the corresponding values for normal tissues. . . .

"g. Tumors tend to converge enzymatically to a common type of tissue. . . ."

Greenstein's generalizations fit in well with certain established biologic facts regarding malignant neoplasms. Despite great variation in their behavior they form a more homogeneous group in respect to their growth potentialities, their cytologic characteristics and their total disregard for the economy of the whole than do normal tissues. Tumors tend to converge biologically to a common type of tissue. Just as some metastases from clinical cancers reproduce the structure of the more anaplastic portions of a primary neoplasm, so do some transplanted tumors appear less well differentiated in successive generations of transplantation

from host to host. In so doing, the neoplastic cells alter their appearance and the enzymatic pattern becomes altered, too. The teleologist might well reason that those enzymes which increase in activity during the process represent those responsible for the growth vigor of the cells and conversely those reduced in concentration represent enzymes concerned with dispensable functions or, at least, those functions subordinate to growth.

In the light of the most recently acquired information, cancer seems best explained as a cellular adaptation to an altered environment as suggested by Rhoads[107] and by the Ayres.[6] Earle exposed cultures of mouse fibroblasts to the presence of the highly carcinogenic hydrocarbon 20-methylcholanthrene (1 microgram per milliliter of culture medium). He described changes in the cells that were more pronounced than in control series to which none of the carcinogen had been added intentionally.[25] Cells exposed to the methylcholanthrene for as little as six days produced sarcomas when transplanted into suitable mice.[26] These tumors had the same growth, structural and chemical characteristics as those arising spontaneously or produced by carcinogenic agents in mice. The frequency with which successive samples of the altered cultures produced sarcomas in mice decreased as the exposure to the agent increased and the histologic pattern of the sarcomas became more irregular.[94] Control cultures also produced sarcomas when grafted into mice. Earle cannot eliminate the possibility that the neoplastic transformation in the control cultures resulted from their accidental contamination with methylcholanthrene but Gey,[33] too, has presented evidence that the carcinogenic agent is not essential to the transformation. No known carcinogens have been used in his laboratory yet cancers have been produced from his cultures of cells grown in roller tubes. The environment of tissue culture is certainly far different from that of the animal body even though growth of some cells occurs. Perhaps the surviving cells of the original explant are the hardiest of the race which have changed their composition to survive. It is well known that the usual products that denote cellular differentiation are formed but rarely *in vivo*—further evidence of the restricted character of growth obtained in tissue culture.

The nature of the environmental change responsible for carcinogenesis is not known. Hyperplastic states may precede cancerous transformation both in man and experimental animals, but other neoplasms apparently arise from morphologically normal tissues. The thesis that malignant tumors do not arise from completely normal cells was first advanced by Billroth. Eschenbrenner and Miller[28] produced hepatomas in mice by feeding carbon tetrachloride. The tumor response increased when the time of administration of a standard dose was increased or when the amount given was increased in unit time. A correlation was found between the degree of liver necrosis and the incidence of hepatic tumors in relation to dose but graded series of necrotizing and non-necrotizing doses indicated that visible necrosis was not necessary to the production of hepatoma.

A series of experiments by workers at the University of Wisconsin may shed some light on one possible mechanism by which a carcinogenic effect may be elicited.[88, 90, 105, 106] Rats fed a diet containing the azo dye, *p*-dimethylaminoazobenzene (butter yellow) develop hepatic tumors. The dye becomes so firmly bound to cellular protein that it may be liberated by tryptic or alkaline hydrolysis but not by boiling organic solvents or by hot trichloracetic acid. The amount of dye bound by the liver cells varies directly with the different carcinogenic potencies of the various C-monomethyl derivatives of the carcinogen. No dye is bound by organs or tissues of rats in which butter yellow does not induce tumors. Low levels of bound dye were found in the livers of mice fed *p*-dimethylaminoazobenzene in which species carcinogenesis proceeds but slowly. No dye was bound by hepatic proteins of species in which the agent produces no liver tumors.

Bound dye reaches a maximum concentration after feeding *p*-dimethylaminoazobenzene and then declines slowly. An inverse relationship exists between the carcinogenic activity of graded doses of the parent substance or of C-monomethyl derivatives of varying carcinogenic potencies and the time required to attain a maximum level of bound dye. The inhibitory effect of riboflavin on the carcinogenic action of butter yellow is reflected in a lower level of bound dye in the liver of rats ingesting the protective diet. Bound dye also disappears more rapidly from the livers of rats eating a riboflavin-rich diet. Bound dyes were not found in hepatomas produced by *p*-dimethylaminoazobenzene though the contiguous hepatic tissue contained it in considerable quantities. This can be interpreted as indicating a difference between the proteins of normal and neoplastic hepatic cells.

It has been established that hepatic neoplasms induced by *p*-dimethylaminoazobenzene contain more desoxypentosenucleic acid than do normal liver cells while the concentration of pentosenucleic acid remains the same or is slightly reduced. Hepatoma formation is accompanied by decrease in hepatic riboflavin. The Wisconsin workers reported that the non-carcinogenic or weakly carcinogenic azo dyes had little or no effect on concentrations of protein, nucleic acids, riboflavin of the liver cells while *p*-dimethylaminoazobenzene and some of its highly carcinogenic homologues caused an alteration in the liver in the direction of that associated with hepatoma. The magnitude of the change could be correlated with the relative carcinogenic potency of the dye fed. Similar data concerning the effect of carcinogenic azo dyes on liver proteins have been published by Griffin, Nye, Noda and Luck.[47]

It has been suggested that the period during which dye-binding increases in the liver represents a period during which the average affected cell can synthesize the proteins to which the dye can attach itself faster than they are removed by dye-binding and in sufficient quantity to permit normal functioning of the tissue. Decrease in the concentration of bound dye with continued dye-feeding suggests that the binding of the dye may have affected specific synthetic mechanisms to such an extent that the combined demands of normal function and removal of protein by the carcinogen cannot be met. Viable cells may finally result which have completely lost those systems controlling normal growth and represent the initial tumor cells.

Evidence that the hydrocarbon 3,4-benzpyrene also becomes bound to proteins in the skin of rodents in which it produces epidermoid carcinoma has been obtained.[91] Benzene solutions of this hydrocarbon were applied on the skin of mice for periods of one to eight days. The mice were killed twelve to sixteen hours after the last application and the crude proteins from epidermis and dermis were collected separately. The crude epidermal protein was hydrolyzed with strong alkali to liberate fluorescent materials after exhaustive extraction with hot ethanol. Similar fluorescent substances could not be obtained from epidermal or dermal proteins of normal or benzene-treated mice nor from the dermal proteins of mice treated with the carcinogen.

The preliminary chromatographic purification of the benzpyrene largely eliminates the impurities in the commercial product from consideration, but the origin of the fluorescent material is complicated by the large number of naturally occurring fluorescent materials. However, the formation of detectable quantities of bound fluorescent material within three hours after a single application of benzpyrene and the progressive increase in the amount of fluorescent material with successive applications indicate that the bound fluorescence is derived from benzpyrene. Furthermore, croton oil, which causes at least as great a hyperplastic reaction, does not give rise to fluorescent material in the epidermis.

The evidence that the fluorescent material is combined with protein rests in part on the methods used for isolating the protein. Additional extractions of the epidermal

protein preparation with hot ethanol, ethyl ether, acetone or benzene did not remove the fluorescent material. Solution of the protein in weak ethanolic alkali liberates only small amounts of the fluorescent material. These findings argue against the possibility that the fluorescent material might be adsorbed only on the protein surface.

Whether or not protein denaturation by binding with other carcinogens is a fundamental step in all carcinogenesis remains to be investigated. The hypothesis is attractive, is supported by the data currently available and might serve to explain the great variety of cancer-producing substances.

Neoplastic tissue has attracted much more interest among investigators than has the body in which it lives. Ewing's great contributions to medicine—the diversity of neoplastic diseases and the correlation of structure of tumors with their biologic behavior—provide a firm foundation for further work. Greene has proposed that the ability of a neoplasm to grow in the anterior chamber of the eye of an alien species be adopted as a criterion of the malignant state.[43,44] Embryonic tissues and a few tumors usually regarded as non-malignant share this property. Perhaps Greene has found a means of segregating the most highly malignant of neoplasms, since the ability of cancers to grow on heterotransplantation indicates a hopeless prognosis. To advocate use of this procedure as a diagnostic test for clinical cancer must imply that malignancy does not vary in degree. Greene states specifically that it does. Other workers[24,27,114] have found that few tumors that are malignant by commonly accepted standards grew on heterotransplantation, even though they killed patients. The delay in growth of some transplants in the anterior chambers of rabbits' eyes for periods of months and the inconsistent behavior of pieces from the same neoplasm in different individual animals of the same species[113] constitute important obstacles to the use of the technic as a test for clinical cancer.[114] No method of diagnosing cancer has yet approached in reliability the histologic examination of tissues by a competent pathologist.

However impractical transplantation technics may be for clinical purposes, they have provided a means of studying an interesting biologic phenomenon. A primary cancer may not grow in the anterior chamber but its metastases may. Moreover, individual metastases vary in their ability to survive transplantation into an alien host. This suggests that neoplasms may go through an evolutionary cycle after their inception. A study of the development of spontaneous endometrial carcinomas in rabbits supports this view.[45] The earliest lesion will not survive transplantation to normal rabbits but will grow on autologous transfer. A later stage may survive transplantation to a normal animal indefinitely but further development does not occur in the new host. Continued residence in the primary host leads to progressive developmental changes that eventuate in cancer. Greene and Newton stress the importance of the host's constitution in permitting the evolutionary cycle to develop.[45]

Some cancers represent cells so altered that they are not subject to any known mechanisms by which the body may restrain their growth. In all probability such neoplasms grow progressively and rapidly. All gradations between this acme of the malignant state and the restrictions of normal growth are encountered in tumors. The work of Huggins in restraining the growth of prostatic carcinoma through altering the hormonal state of the body by castration or estrogenic therapy need not be detailed here. The growth of certain animal tumors may also be influenced by definite agents. Interstitial cell tumors produced in mice by estrogens fail to grow when transplanted into the subcutaneous tissues of mice of the same strain in which the tumor arose unless the recipient is estrogenized.[38] The grafts may lie dormant for months but then will grow vigorously if estrogen be given. A transplantable lymphosarcoma in mice may regress if the animal's diet is deficient in

riboflavin or contains an anti-metabolite of riboflavin.[128] Voegtlin and Thompson found that growth of initially small hepatomas was rapid in some Osborne-Mendel rats but regressed in others.[132] The diet fed was adequate in all respects for growth of young rats and included a daily supplement of 400 mg. of brewers' yeast. Some hepatomas undergoing regression, and sometimes even tumors that were no longer palpable, grew progressively after the addition of 200 to 3,200 micrograms of riboflavin or 4 to 20 micrograms of biotin to the daily yeast supplement. A combined riboflavin-biotin treatment provided better stimulation than either of the vitamins alone. This striking effect could not be accounted for by an increased consumption of calories or protein and was tentatively attributed to an influence of the vitamins on intermediary tissue metabolism. The authors suggested that the growth differential of malignant and non-malignant tissues in the same host organism depends on a nicely balanced function of certain dietary factors, which may produce either gain or loss of weight of these tissues, more or less independent of each other. Better definition of factors responsible for tumor growth may serve as an important means for better control of clinical cancer.

The effects that malignant neoplasms produce on the economy of their hosts has received little attention until recently. A better understanding of the tumor-host relationship has immense potential value for the clinician. Neoplastic diseases may kill their hosts solely because they produce anatomic defects that are inconsistent with life. These lesions prevent proper function of some vital structure whether or not they be produced by cancer cells or scar tissue. Surgeons and radiologists have become more skillful in eradicating primary malignant neoplasms so that a large fraction of cancer patients die of their metastases. It is difficult to understand why the metastatic cancers found in the average cancer patient at necropsy should be fatal because of their anatomic distribution. Massive hepatic involvement, for example, is rarely associated with a terminal syndrome that may be ascribed to failure of the liver's functions. A considerable proportion of the mortality from various cancers, then, must be due to profound changes in the host's economy that may be defined in terms of pathologic physiology.

It is generally agreed that most cancer patients have a significant degree of hypoalbuminemia as determined by electrophoresis in the Tiselius apparatus.[87,99,101,118] The hypoalbuminemia in gastric cancer patients usually persists despite an adequate intake of nitrogen and calories and in the presence of positive nitrogen balance.[56] Albumin is the last of the plasma proteins to return to its normal concentration after successful eradication of the gastric cancer. Other non-neoplastic lesions of the gastrointestinal tract do not produce hypoalbuminemia so refractory to remedial procedures. Hypoproteinemia may be moderate to pronounced in late cancer. The concentrations of the various plasma proteins were determined in a large group of patients representing various anatomic types of cancer, excepting plasmacytomas, and great diversity in the extent of their disease.[87] Hypoalbuminemia was found in people with small localized cancers and became progressively more pronounced as the extent of neoplastic involvement increased. Total proteins fell more slowly than did albumin, indicating concomitant increase in the total globulin fraction. Each of the globulins contributed to the increase in some cases but the concentration of electrophoretic fibrinogen was increased disproportionately, alpha globulins increased proportionately and beta and gamma globulins lagged behind the others. The degree of change in globulin fractions increased with extent of disease and was not statistically significant in patients with localized cancers. Late cancer was sometimes associated with concentrations of gamma globulins lower than in healthy adults, as Seibert, Seibert, Atno and Campbell reported.[118] The type of alteration in

the plasma proteins seemed to be relatively constant among different anatomic types of cancer with minor variations. Petermann, Karnofsky and Hogness,[99] for example, reported higher concentrations of gamma globulin among patients with Hodgkin's disease than was usually found in leukemia or lymphosarcoma.

The profound changes in the plasma proteins of patients with plasma cell myeloma seem to be unique. An excellent description of the electrophoretic changes in the plasma of these patients has been presented.[4] The alterations when present are sufficiently characteristic to form the basis for diagnosis of multiple myeloma in the absence of the usual changes seen in roentgenograms of the affected bones. Close correlation between the plasma protein abnormalities and cellular alterations in the bone marrow was found.

Abnormal plasma proteins are encountered rarely in patients with other forms of neoplastic diseases when electrophoresis is conducted at pH 8.5. Petermann and Hogness[100] reported that the plasma of patients with gastric and pulmonary cancers contained a significantly greater amount of a rapidly migrating acid protein when analyzed by electrophoresis in acetate-chloride buffer at pH 4.0. It is probable that this substance is related to plasma mucoproteins described by Winzler[135,136] which appear in higher concentrations in people with several different diseases including cancer.

The reasons for the disturbance in plasma proteins among cancer patients are not clear. The changes are similar to those seen in plasma of patients suffering from other wasting diseases. This need not imply that the fundamental process responsible for the alteration be identical in all patients with malignant neoplasms nor in cancer, tuberculosis and similar wasting states. Taylor, Mickelsen and Keys[130] have shown that malnutrition in the sense of simple caloric restriction is not necessarily accompanied by hypoalbuminemia. The pronounced anorexia so commonly associated with advanced cancer suggests that malnutrition may play a significant role in accelerating the progress of cachexia in cancer patients.

The changes in plasma proteins though characteristic of the cancerous state are by no means pathognomonic. These and more subtle alterations in blood proteins have been discussed by Huggins[59] who believes that the data imply a defect in serum albumin which is not specific for cancer as it also occurs in infections. Deficient thermal coagulability of cancer serum may be demonstrated by measuring its inhibition by iodoacetate. A test has been devised by Huggins, Miller and Jensen[60] which relates the smallest quantity of iodoacetate required to prevent coagulation of serum by heat to the protein content of the serum. These workers reported that all of eighty-five consecutive cases of clinically active cancer had low indices whereas only sixteen of ninety-five patients with non-cancerous diseases had indices of the same order of magnitude. Further experience is necessary before the clinical usefulness of this procedure may be evaluated finally. Certainly it is not a specific test for cancer at this time. Other changes in the blood of cancer patients have been proposed as bases of diagnostic tests for cancer.[13,14,55,95,108] The effectiveness of those that have been investigated thoroughly is questionable.[82,122]

Evidence that an appreciable proportion of patients with gastrointestinal cancers have some hepatic dysfunction has been presented.[1,2,5] Tagnon and Trunnell[129] found that the incidence of abnormal liver function tests was not higher among patients with operable mammary cancer than among a group of apparently healthy adults. The proportion of abnormal tests was higher in a group of patients with inoperable, metastatic cancer of the breast. The abnormal findings could not be attributed to liver metastases in all instances.

Patients with gastric cancer have some disturbance of carbohydrate metabolism, too.[3] Intravenously injected glucose disappears more slowly from their blood than from normal persons or people with non-neoplastic lesions of the stomach. The glyco-

gen content of the liver after a ten-hour preoperative fast is the same in these three groups of patients; but if glucose is given preoperatively, the increase in the concentration of hepatic glycogen is much smaller than in the control groups. The deficiency in hepatic glycogenesis can be corrected by giving large doses of adrenocortical extract which, however, does not alter the glucose tolerance curve.

Dobriner and his colleagues[23] have devised methods for isolating and identifying a number of steroid hormones and the by-products of their metabolism quantitatively from the urine. New compounds have been described. Excretion patterns determined for several different physiologic and disease states indicate that the types of substances excreted by cancer patients differ in some respects from those found in pregnancy, Cushing's disease and adrenal hyperplasia. Whether or not these observations deal solely with the effects of neoplasms on their hosts is conjectural. One compound, Δ^9 etiocholenolone, a metabolite of an adrenal cortical precursor, may be found in the urine of cancer patients but is rarely present in the urine of normal subjects. It was found in the urine of two people who subsequently developed cancer. Perhaps some physiologic abnormality associated with carcinogenesis may be reflected in the excretion pattern of these substances.

The examples cited do not represent a complete résumé of the metabolic defects that have been described among cancer patients. Much more work must be done before one may understand the reasons for these aberrations and present an integrated picture of the pathologic physiology of neoplastic growth.

Profound effects produced on the host by transplanted neoplasms have been described. These tumors usually grow as solitary localized globular masses in the subcutaneous tissues of the axillary or inguinal regions. Macroscopic metastases are rarely found with the tumors used and the growth is circumscribed rather than infiltrative. It is safe to assume then that the effects observed are not produced by the presence of any appreciable number of tumor cells in a vital structure.

Catalase, a peroxide-splitting ferment, is considerably reduced both in the livers and kidneys of tumor-bearing rodents and the degree of reduction increases as the tumor grows larger.[46] Removal of the neoplasm results in a prompt restoration of catalase to its normal level. A similar effect was not observed in pregnant rats or in rats in which a brei of embryo tissues had been implanted. Despite this profound effect in the liver and kidney catalase, the catalase of the erythrocytes remained normal. *d*-Amino acid oxidase is also decreased in the livers of some tumor-bearing rodents due to diminution in concentration of the protein apoenzyme rather than the flavin-containing co-enzyme.[74] Hepatic and renal arginase, hepatic riboflavin, tissue esterases and lipases are also reduced in tumor-bearing rodents.[46] The mechanism of reduction of these various enzyme systems in the cancer's host is not known. L. L. Miller[98] has shown that rats lose hepatic catalase, alkaline phosphatase, xanthine dehydrogenase and cathepsin when fasted for seven days. The loss of enzyme parallels or exceeds the loss of liver protein, indicating a loss of enzyme protein *per se* rather than enzyme activity. Seifter and his co-workers[119] reported that the concentration of hepatic nicotinic acid, riboflavin, *d*-amino acid oxidase and arginase is diminished in rats fed a protein-free diet. These observations suggest that the neoplasms that have been investigated may mediate the changes observed in liver composition through some mechanism involving malnutrition though the possibility of a specific humoral mechanism has not been entirely eliminated.

The progressive growth of Walker carcinoma 256 is associated with pronounced anorexia in the rats in which the tumor grows even though they eat freely a semi-synthetic diet which permits growth, pregnancy and lactation in normal rats. Many of the tumor-bearing rats maintain their body weight or increase it steadily for

considerable periods of time despite the decrease in alimentation. As the tumors grow larger the rat carcasses grew smaller. The ability of the tumor-bearing rat to maintain or increase its weight reflects a pronounced increase in the water content of the neoplasm. This is further borne out by the observation that normal rats of the same age, weight and sex ingesting identical amounts of the same diet eaten by a tumor-bearing rat fail to gain and eventually lose weight. The weight lost from the carcass (rat minus tumor) of the cancerous rat exceeds that lost by its pair fed control.[85]

F. R. White has shown that a transplanted mammary adenocarcinoma will grow in mice even though they eat a diet containing almost no nitrogen.[134] Ball and Samuels described redistribution of body nitrogen in hypophysectomized rats in which the Walker tumor grew progressively.[7] Building blocks must have been acquired from body tissues under these circumstances. It now appears that large Walker tumors usually contain more nitrogen than was stored by their hosts during the period of tumor growth even though the diet ingested was qualitatively adequate.[85]

It was assumed that those tissues that lost nitrogen to the body pool represented potential sources of tumor nitrogen. A study of the nitrogen content of heart, liver, spleen, kidneys, lymph nodes and residual carcass of tumor-bearing rats and their pair fed controls showed that those organs and tissues which usually lose nitrogen under conditions of simple starvation also lost nitrogen during tumor growth, excepting the spleen and liver. The spleen increased its mass, probably as a result of extramedullary myelopoiesis known to occur in tumor-bearing rodents, until late in the period of tumor growth when it usually became quite small. The liver hypertrophied soon after the neoplasm commenced to grow but it, too, lost nitrogen when it approximated 35 to 40 per cent of the body weight and sometimes became even smaller than the liver of the pair fed control.[120] It is well known that tumor-bearing rats develop large livers but the tendency for the hypertrophy to disappear has been referred to but once previously.[84] Apparently this change reflects some alteration in the metabolism of the tumor-bearing host.

It was found that the total lipid concentration of both the rat carcass and the tumor fell progressively as the Walker carcinoma grew. The fat lost from tumor-bearing rats exceeded that lost by pair fed normal rats of the same age, weight and sex.[86] The excess loss of lipid indicates a loss of calories accomplished either through the failure of the tumor-bearing rat to obtain the potential caloric value of its foodstuffs or to the initiation within the rat's body of some process associated with the growth of the neoplasm which requires the additional expenditure of energy.

These experiments cannot be translated to the cancer patient at the present time but they suggest certain reasonable lines of approach to the problem. Anorexia is a common phenomenon among patients with considerable amounts of cancer and emaciation is too familiar a phenomenon to require elaboration. The cachexia in cancer has never been adequately explained.

It has become increasingly apparent that a few patients with cancer are able to survive and lead useful healthy lives for periods of years after excision of a tumor and then to die of metastases of the same tumor for which operation was performed. The metabolic picture among these patients must be somewhat different from those whose disease pursues a relentlessly progressive course. If a combination of immunologic investigation and metabolic studies could determine the differences in these two groups of patients, a long stride toward the effective control of neoplastic diseases will have been made.

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Combined Staff Clinics

Inborn Errors of Metabolism

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. JOHN V. TAGGART: The term "inborn errors of metabolism" was coined by Sir Archibald Garrod in his now famous Croonian Lectures before the Royal College of Physicians in 1908.[1] Garrod at that time recognized only four distinct disturbances of metabolism which could justifiably be classed as inborn errors, namely, albinism, alcaptonuria, cystinuria and pentosuria. Certain features common to these anomalies were the basis for inclusion in this group. First, the onset of the characteristic abnormality could be dated to the first few days or weeks of life, at least in certain of the cases and especially when a particular effort was made to do so; in some instances, notably in alcaptonuria, this was relatively easy because the dark-staining property of the infant's urine attracted attention shortly after birth. A second characteristic of the inborn errors was their familial occurrence in a considerable number of cases. The earliest clinicians interested in these disorders noted the frequency with which they occurred in the offspring of consanguineous marriages, a condition which we now recognize favors the appearance of a recessive trait. Lastly, these metabolic disturbances were of a relatively benign and non-progressive character and consequently were compatible with long life.

As one would anticipate, these are abnormalities rarely encountered. If their only attraction lay in the clinical problems which they present, we might be inclined to regard them as little more than interesting sports of a capricious Nature. Fortunately, certain far sighted clinicians of the 19th century saw in these cases opportunities for unravelling various aspects of intermediary metabolism and intensive study of them ever since has added considerably to our understanding of the normal metabolic processes.

The excretion or deposition in tissues of some unexpected compound can be imagined to occur as the result of one of the following circumstances: (1) a normal metabolic intermediate is produced in such excessive quantities that the biochemical processes by which it is disposed of are unable to cope with the load; (2) metabolism may be diverted into useless or dead-end pathways yielding products incapable of undergoing further chemical change or (3) there is an interruption in the normal sequence of metabolic reactions leading to the accumulation of a normal intermediate in some tissue or body fluid. Time does not permit considering each of these possibilities in detail. Suffice it to say that the last appears to be by far the most acceptable in the light of our present knowledge. However, it should be emphasized that the isolation or identification of even major intermediates in the rapidly moving stream of normal metabolism is frequently impractical because of the minute quantities which are present at any moment. It is in this respect that individuals with inborn errors may provide valuable information concerning the nature of certain metabolic intermediates.

Another aspect of this problem is of great importance. The familial occurrence of these disorders directs our attention to the role which heredity plays in determining the chemical composition of all living cells and the manner in which this is achieved. The clinical observers of inborn errors have con-

[1] GARROD, A. E. Inborn Errors of Metabolism. London, 1909. Henry Frowde.

scientiously collected and analyzed geneologic data from their cases. In many instances it has been possible to arrive at certain general conclusions regarding the transmission of the defects even though the data collected in the vast majority of cases lack both the quantity and quality desired by the geneticist. From this genetic approach there has arisen in recent years a new and extremely productive type of investigation, that dealing with the nature of the genetic control of biochemical reactions. We particularly associate with these studies the names of Beadle, Tatum and Bonner. Dr. David Bonner of the Department of Microbiology at Yale has been good enough to come here to tell us something of this recently developed field of investigation which, as will become apparent, attacks the problem of inborn errors of metabolism at the most basic level.

DR. DAVID M. BONNER: The subject which Dr. Taggart has introduced centers primarily around the general problems concerning the mechanism of the hereditary control of cellular metabolic processes. Before entering into a discussion of this subject I believe that it might be well to consider what genes are and what their general properties are.

By definition we know that genes are the smallest units of inheritance and are arranged in linear fashion on a gross cytologic unit, the chromosome. A little information concerning the chemistry of genes is available, primarily the fact that they are composed of nucleoprotein. One fundamental property of the gene is associated with its nucleoprotein nature, namely, its ability to undergo self-duplication. Stated in another way, each gene is capable of catalyzing the production of a unit exactly like itself. Another property of the gene, and a property with which we will be concerned, is its mutability. Genes may undergo change or mutation, and this altered or mutated gene is then subsequently duplicated. Indeed it is this property of mutation which has enabled us to characterize genes since genes can be recognized only after a change has occurred with a concomitant loss of function. The problem we are faced with in a discussion of inborn errors, however, is the question of what genes do and how they control specific heritable traits.

Stemming from the work of Garrod many years ago, and from the works of investigators using the fruit fly and maize, strong support was obtained for the view that genes control gross morphologic characters by determining what biochemical reactions might occur within a cell. As a test of the hypothesis that genes do control biochemical reactions, Drs. G. W. Beadle and E. L. Tatum at Stanford University initiated work with the pink bread mold, Neurospora crassa.[2] This organism grows ordinarily as branched hyphae. The vegetative hyphae give rise to multinucleate asexual spores known as conidia which, when transferred to fresh medium, give rise again to the original vegetative strain. These vegetative strains are haploid. The diploid stage of the organism is transient and is brought about by fusion of a conidium of one mating type with a protoperithecium of a strain of opposite mating type. The strains of opposite mating type appear identical and can be distinguished only by the fact that when the two strains are grown together fruiting bodies form. The fusion nucleus resulting from the fusion of the two nuclei of opposite mating types undergoes two meiotic divisions and one mitotic division, thereby giving rise to eight haploid ascospores. These spores after activation give rise again to haploid vegetative cultures. Thus from a genetic standpoint this organism is exceptionally easy to work with since all the products of meiosis are preserved. The fact that the vegetative strains themselves are haploid is of great aid since problems of dominance are of no concern. Lastly, this organism can be grown on a simple synthetic medium. The parental strain requires a carbon source such as sucrose, a nitrogen source such as ammonium nitrate, inorganic salts and the one organic growth factor, biotin.

[2] See reviews by BEADLE, G. W. *Physiol. Rev.*, 25: 643. 1945 and BONNER, D. M. *Science*, 108: 735, 1948.

As a test of the general hypothesis that genes do indeed control biochemical reactions, it was argued that it should be possible to induce gene mutations affecting the synthesis of such vital cellular substances as vitamins and amino acids and that these mutations in turn could be detected as an increased complexity of growth factor requirements. An experiment was accordingly carried out as shown in Figure 1. Conidia were treated with ultra-violet light, an agent known to increase mutation rate in other organisms. Since conidia are multinucleate, these treated spores were crossed with the opposite mating types of the parental strain to permit segregation of genetic characters. Single ascospores were picked from the resulting cross. To insure growth of spores having increased nutritional requirements the spores were germinated on a medium containing a crude source of vitamins and amino acids. These isolated strains, that were capable of growing on a complex medium, were next tested for their ability to grow on a simple medium capable of supporting the growth of the parental strain, that is, a medium containing only sucrose, nitrate, inorganic salts and the one vitamin biotin. Of the strains tested, 1 to 2 per cent were found which would grow on the complex medium and not on the simple medium. The factor necessary for the growth of such strains was determined by a straightforward series of tests as shown in Figures 1 and 2. Such strains were tested on minimal medium plus all the amino acids as well as the minimal medium plus all the known vitamins. In the instance used in Figure 1 one finds that growth occurs only in the tube to which all the known vitamins had been added. From here it is simply a process of running down the single components of this vitamin mixture. (Fig. 2.) In the instance used in Figure 2 pantothenic acid is the additional factor required for growth. Thus by means of gene mutation we now know that it is possible to obtain strains which differ from the parental strain by having an added growth factor requirement.

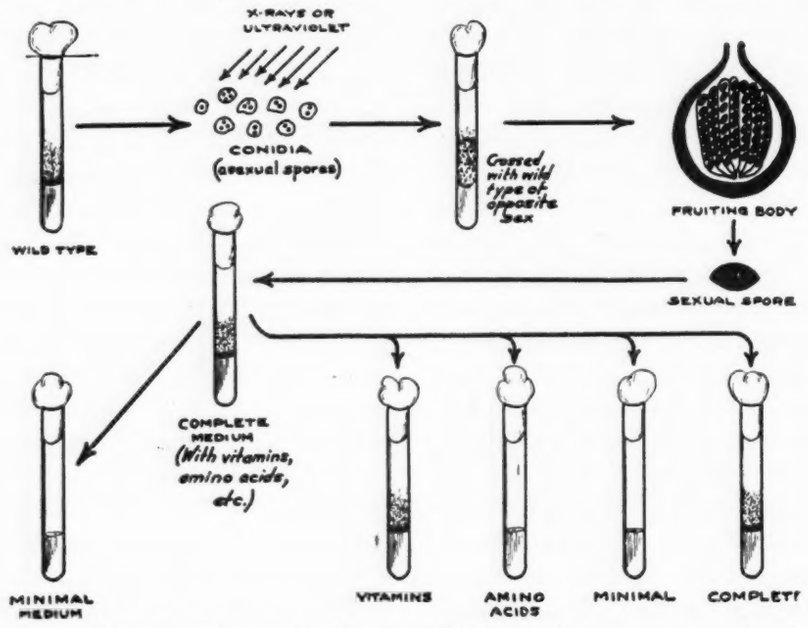

FIG. 1. Experimental procedure by which biochemical mutants are produced and detected in Neurospora.

One might next logically inquire whether this requirement for pantothenic acid is a hereditable trait. It is possible to put this to a very simple and straightforward test. If one crosses this mutant strain with the opposite mating type of the parental strain, Mendelian segregation of the mutant nuclei should occur. The eight ascospores con-

tained in a single ascus of the mature fruiting body are dissected out in order and germinated. (Fig. 3.) The resulting eight cultures all grow on a medium containing pantothenic acid; while if we test them on a medium containing no pantothenic acid, only four will grow, that is, four of the eight cultures resulting from the cross require pantothenic acid for growth while the remaining four do not. The requirement for pantothenic acid segregates, therefore, as a 1:1 ratio, as would be expected in the segregation of a single gene difference. Thus the requirement for pantothenic acid results from a single gene difference between parental type and the mutant strain, i.e., alteration of a single gene has resulted in the loss of ability to synthesize the vitamin, pantothenic acid. In the course of the past seven years mutants for nearly all the known vitamins and for nearly all the known amino acids have been obtained. While not all of these strains have been investigated genetically, those that have been so investigated differ from the parental strain by alteration of a single gene. Gene control, therefore, is not restricted to pantothenic acid synthesis but is known for a great many vital cellular

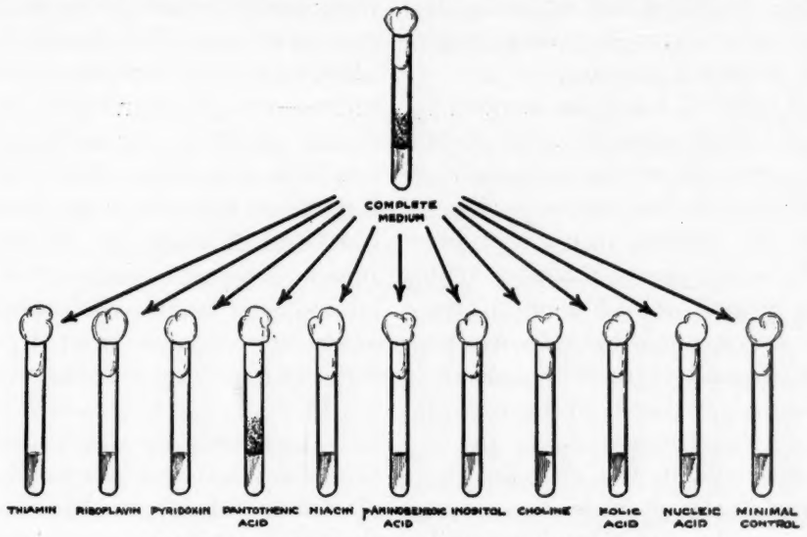

FIG. 2. Tests of mutant strain on individual vitamins.

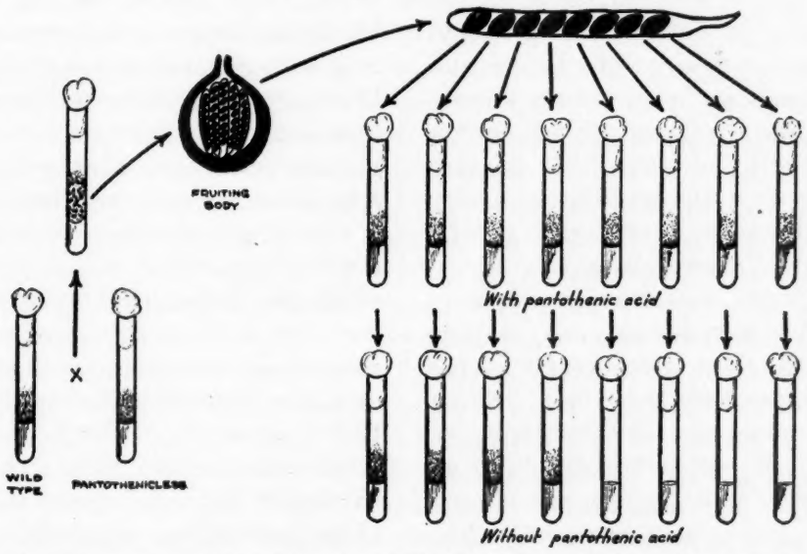

FIG. 3. Experimental procedure by which the inheritance of a mutant type is determined.

constituents. It might be pointed out that this type of technic is limited in that one can detect only mutations for those compounds which can be added to the cells from the media. We are largely restricted, therefore, to detecting mutations involving small molecules such as vitamins and amino acids rather than the mutations involving large molecules such as intact proteins.

The material which I have just reviewed tells simply that loss of a specific gene gives rise to loss of a particular synthetic capacity. Let us next examine the biochemical consequences of this loss. Several mutant strains are known which require the amino acid tryptophan for growth. All of these strains are known to differ genetically from the parental strain. Do all of these strains require tryptophan as a result of the loss of the same gene or may the loss of any one of several genes give rise to the requirement for this amino acid? It is possible by genetic methods to answer this question. Two mutant strains genetically identical when crossed together give only mutant progeny. However, if the two strains differ genetically and if the genes in question are not closely linked, wild type progeny would be expected occasionally as a result of crossing over. When the tryptophan-requiring strains are crossed with each other, four genetic classes are found. Alteration of any one of four separate genes, therefore, gives rise to loss of tryptophan synthesis. Let us now inquire whether these four genetic types may not be correlated with four distinct reactions necessary for the synthesis of tryptophan. All of the tryptophan-requiring strains will grow when given this amino acid. Not all will grow, however, when given the biologic precursor indole, and indeed still fewer will grow when given the biologic precursor of indole, anthranilic acid. Since no strains are known which will grow on indole but not on tryptophan and since no strains are known which can grow on anthranilic acid but not on both indole and tryptophan, the sequence of reactions is established as anthranilic acid → indole → tryptophan. These tryptophan-requiring mutant strains may, therefore, be broken up into at least three biochemical classes. The conversion of indole to tryptophan is known to occur in a single step, by the condensation of indole with the amino acid serine. One must then conclude that those strains which grow on tryptophan but cannot grow on indole are blocked in their ability to carry out the reaction indole + serine → tryptophan. We have in this instance, therefore, shown that because of the loss of a particular gene the organism no longer has the ability to carry out a known biochemical reaction. Investigations with many different strains have shown that compounds such as vitamins and amino acids are characterized by a sequential series of reactions necessary for their synthesis. In many instances we have been able to locate precisely the exact biochemical reaction which has been lost as the result of genic alteration, as I have just discussed in the case of the conversion of indole to tryptophan. Other mutant strains, such as those blocked in their ability to convert anthranilic acid to indole, reflect simply our inadequate knowledge of cellular biochemistry. As our knowledge in this field increases, these mutant strains will also be shown to represent loss of specific reactions, I am sure.

One might now say, with a comfortable degree of assurance, that single genes control single biochemical reactions. This in itself, however, tells us little concerning the actual mechanism involved. Can we probe more critically into the relationship existing between gene and biochemical reaction? Nearly all biochemical reactions are known to require the presence of a specific enzyme. Does genetic loss of biochemical function result from loss of substrate necessary for enzyme activity, or from loss of the enzyme itself? Our information in this regard is unfortunately scanty. Many instances are known in which precursor accumulation results from genetic blocking. For instance, those strains which can grow on tryptophan and indole but not on anthranilic acid accumulate anthranilic acid in the medium. In these cases, therefore, loss of substrate

has not occurred. With regard to enzyme loss, few cases have yet been investigated. The enzyme necessary for the condensation of indole and serine has been described by Umbreit, Wood and Gunsalus.[3] Mitchell and Lein[4] have found this enzyme lacking in the mutant strain unable to grow on indole. Thus we have in this one instance the correlation of a single gene alteration giving rise to loss of ability to carry out a specific biochemical reaction, with the concomitant loss of a specific enzyme. A similar correlation appears to hold regarding the ability of Neurospora to utilize the carbohydrate lactose. Wagner,[5] however, does not find such a correlation in the case of certain pantothenic acid-requiring strains. Thus while in two instances gene alteration leads to enzyme loss, proof that this is a general phenomenon awaits further work.

How might one then sum up current thought in this field? The work which I have just reviewed clearly demonstrates the genetic control of biochemical reactions. Indeed there is a striking correlation between alteration of a single gene and loss of a single biochemical reaction. There is also a correlation between enzyme production and genes. Whether there is a correlation to the extent that single genes determine the specificity of single enzymes seems unlikely. What the precise relationship is, however, between gene and enzyme remains at present an enigma.

In considering the problem of the genetic control of biochemical reactions I have discussed only the fungus Neurospora. I should like now to consider the problem in relation to inborn errors of man. In the first place, I should like to emphasize that the genetic control of biochemical reactions is not restricted to fungi. Indeed Garrod many years ago established that metabolic defects in man are heritable. Available evidence suggests, in fact, that the mechanism of gene action is essentially similar in all living matter. Metabolic pathways in man must therefore be under gene control.

Gene alteration in man would be predicted to lead to metabolic disturbances similar to those found in Neurospora. Accumulation of the intermediate prior to the block would be expected, and indeed is found in the accumulation of homogentisic acid in alcaptonuria and phenylpyruvic acid in phenylpyruvic oligophrenia. This accumulation may occur without harm to the organism, or it may lead to secondary disturbances as is known in the case of certain isoleucine-requiring strains of Neurospora[6] and in the case of phenylpyruvic oligophrenia. Accumulation of an intermediate is not an invariable consequence of gene change; it may be abnormally metabolized. Thus I want to point out that genetic loss of a biochemical function leaves an organism that is never entirely identical with its parental type, since the fate of intermediates which cannot be normally metabolized must be borne in mind. Related to this problem is the thought that gene mutation does not lead to an inactive gene. While the gene is inactive as concerns a particular reaction, it probably controls the production of enzyme with altered specificity and this altered enzyme may in turn prove beneficial or harmful. Thus gene mutations, while giving rise to loss of specific biochemical reactions, at the same time permit new reactions and new metabolic interactions to occur. These many associated problems must be borne in mind when considering the problem of inborn errors in man.

As I mentioned earlier, the vegetative strains of Neurospora are haploid. Since man is diploid problems of dominance must be considered. The diploid stage of Neurospora is transient and cannot be used to investigate this problem. However, without detailed discussion let me simply say that by an indirect method we find all of the characters which I have been discussing recessive. The ability to carry out a given biochemical reaction appears, therefore, to be dominant. Thus while spontaneous gene

[3] Umbreit, W. W., Wood, W. A. and Gunsalus, I. C. *J. Biol. Chem.*, 165: 731, 1946.

[4] Mitchell, H. K. and Lein, J. *J. Biol. Chem.*, 175: 481, 1948.

[5] Wagner, R. P. *Proc. Nat. Acad. Sc.*, 35: 185, 1949.

[6] Bonner, D. M. *J. Biol. Chem.*, 166: 545, 1946.

mutation gives rise to these characters with a certain frequency, the appearance of such characters in the human population is relatively infrequent since the homozygous state would be necessary for expression of these characters.

If we assume that all enzymes are under gene control, many people have wondered whether an ordinary cell or an ordinary man has sufficient space to hold the numerous genes necessary for all the reactions that occur. Geneticists have given us an estimate of about 10,000 genes per organism. They might be off by a factor of 2 or 5 but whether it is 10,000 or 50,000 is not material. If one considers the number of reactions that could be carried out with 10,000 enzymes, one would likely conclude that 10,000 genes are ample for an ordinary organism.

DR. TAGGART: We are indeed grateful to Dr. Bonner for this lucid presentation of a complex problem. The remainder of the clinic will be devoted to the presentation of certain representative inborn errors of metabolism. It is quite fitting historically that the first condition to be presented is alcaptonuria. Dr. Morton Galdston of the Department of Medicine at New York University has had the good fortune to observe several alcaptonurics over a period of years and has kindly consented to tell us of his experiences with these patients.

DR. MORTON GALDSTON: Alcaptonuria is a disorder caused by a defect in the metabolism of the amino acids, tyrosine and phenylalanine, characterized by the excretion of homogentisic acid in the urine. There is abundant evidence that it represents an inherited recessive trait present at birth.

Alcaptonuria is only one of several known disturbances in phenylalanine and tyrosine metabolism, others being phenylpyruvic oligophrenia and tyrosinosis. Phenylpyruvic oligophrenia, which involves only phenylalanine, occurs in certain mentally deficient individuals who excrete phenylpyruvic and phenylacetic acids and phenylalanine. There is some evidence based on animal experiments that thiamine participates in the oxidation of phenylpyruvic acid but this compound has no beneficial effect in phenylpyruvic oligophrenia. Tyrosinosis, of which but one instance has been reported, is believed to be due to inability to oxidize p-hydroxyphenylpyruvic acid, a derivative of tyrosine. It is characterized by the excretion in the urine of tyrosine and p-hydroxyphenylpyruvic acid. The relationship of alcaptonuria to phenylpyruvic oligophrenia and tyrosinosis is shown in Figure 4.

A metabolic derangement resembling alcaptonuria can be induced in guinea pigs maintained on a diet deficient in ascorbic acid and rich in phenylalanine or tyrosine.[7] In addition to homogentisic acid, p-hydroxyphenylpyruvic and p-hydroxyphenylacetic acids are excreted in the urine. Premature and full term infants may also exhibit a disturbance in the metabolism of tyrosine and phenylalanine on a diet rich in protein or large amounts of phenylalanine or tyrosine; the urine contains p-hydroxyphenylpyruvic and p-hydroxyphenylacetic acids but no homogentisic acid.[8] The fact that ascorbic acid prevents these induced metabolic derangements and not the inherited type of alcaptonuria indicates that there is a basic difference between the two, the induced disorders resulting from the overloading of an enzyme system in which ascorbic acid may play some role.

In the inborn type of alcaptonuria homogentisic acid is the only abnormal substance excreted in the urine. It imparts certain chemical properties to the urine which I shall demonstrate in a specimen voided by a ninety-four year old female patient who is now on the New York University Medical Service of Goldwater Memorial Hospital. The color of the freshly voided urine is not unusual if it is acid in reaction; if alkaline it appears brown or black. When a specimen stands exposed to air, it gradually darkens at its upper surface and in time becomes black throughout. Of interest, particularly when the appearance of the urine is normal, are the reactions with Benedict's solution

[7] SEALOCK, R. R. *Federation Proc.*, 1: 287, 1942.

[8] LEVINE, S. Z. The Harvey Lectures, p. 303, 1946–1947.

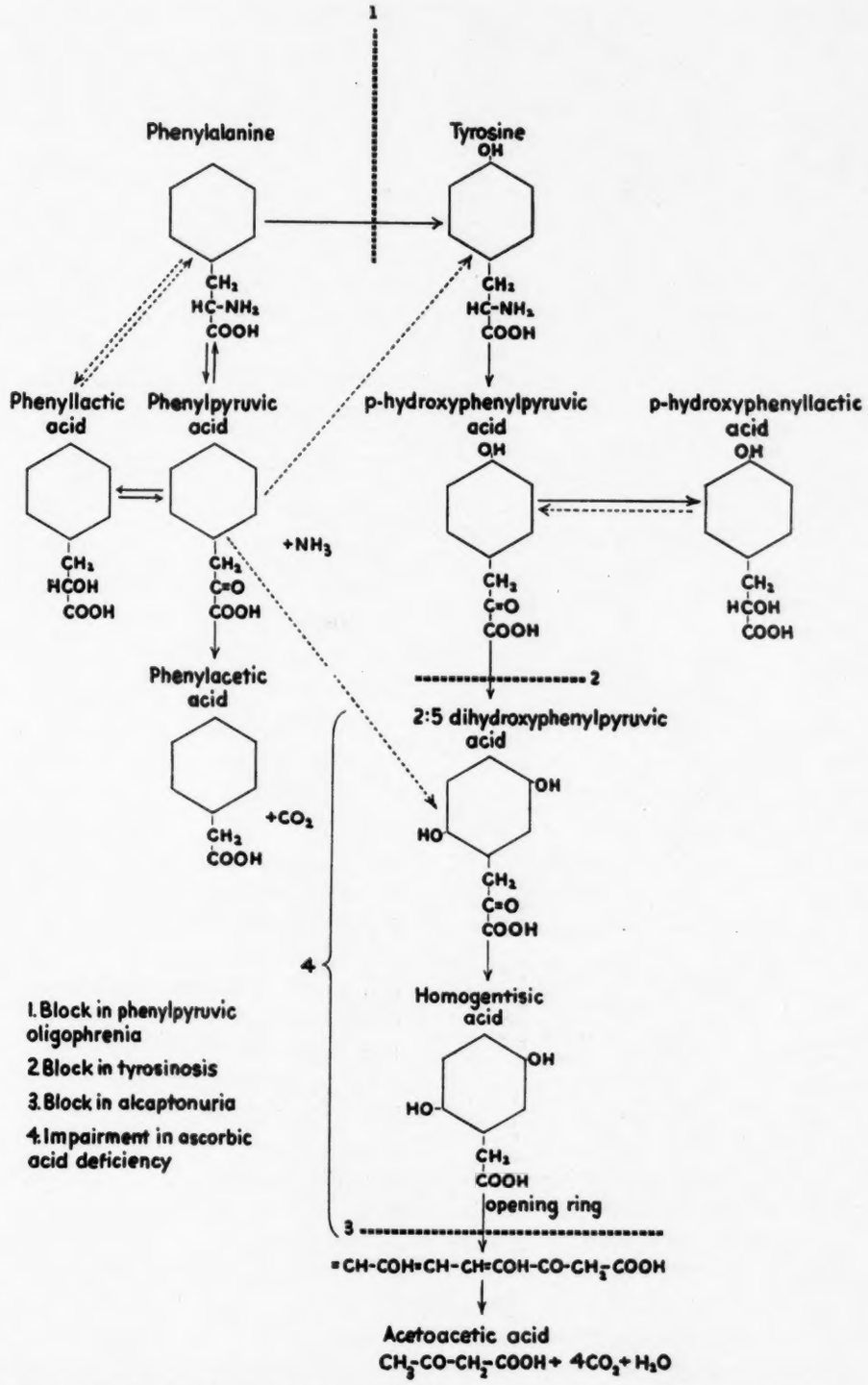

FIG. 4. Metabolic pathways of phenylalanine and tyrosine, indicating sites of block in alcaptonuria, phenylpyruvic oligophrenia, tyrosinosis and ascorbic acid deficiency; modified after Peters, J. P. and Van Slyke, D. D. Quantitative Clinical Chemistry Interpretations, Volume 1, page 766, 2nd ed. Baltimore, 1946. Recent studies by Neuberger et al.[9] suggest that tyrosine is normally first oxidized to 2:5-dihydroxyphenylalanine prior to the formation of 2:5-dihydroxyphenylpyruvic acid.

FIG. 5. Pigment deposition in sclera in alcaptonuria.

and ferric chloride. Homogentisic acid reduces Benedict's solution giving rise to a yellow precipitate and a brown or black supernatant fluid. Failure to differentiate this reaction from that due to glucose may suggest the erroneous diagnosis of diabetes mellitus, as was made in one of the patients whom we studied some years ago. However, homogentisic acid can readily be differentiated from glucose by its failure to undergo fermentation with yeast and by its lack of optical activity. When ferric chloride is added dropwise to the urine, an evanescent blue color appears rather than the Bordeaux red produced by diacetic acid. When strong alkali is added and the specimen is shaken, it promptly turns dark. The term alcapton, which means an affinity for alkali, was derived from this reaction. All of the above reactions are presumptive evidence of alcaptonuria. Isolation of homogentisic acid from the urine is the only certain method of establishing the diagnosis.

Now to come to some of the interesting clinical features of alcaptonuria. It is relatively rare; approximately 200 cases have been reported. It is compatible with long life; witness the ninety-four year old female whom we now have under observation. It is present from birth as may be noted by examination of the urine. There are no other clinical manifestations until the individual reaches about the second or third decade when signs of ochronosis may develop. The term ochronosis refers to the pathologic deposition of a black pigment in cartilage, fibrocartilage, fibrous tissue, tendons and atheromatous areas. The pigment is believed to be a polymer of homogentisic acid. Clinically, ochronosis is manifested by light brown or slate gray pigment in the sclera on either side of the corneal limbus (Fig. 5) and by a bluish discoloration of the ears. Those portions of the ear cartilages containing pigment do not transmit light and feel thick and inelastic. In some instances a bluish discoloration may be noted in the superficial muscle tendons of the hands and nasal cartilages and brown pigmentation is seen in the skin and nails. Necropsy reveals black pigment deposits in the tracheal, laryngeal and vertebral cartilages, in the chordae tendinae at their attachments to the papillary muscles, and in atherosclerotic plaques in the heart valve leaflets and blood vessels. Not infrequently black pigmented stones are found in the genitourinary tract.

By the time alcaptonuric individuals reach middle age they generally complain of pain and stiffness in the large joints due to a deforming arthritis. The spine becomes rigid, there is kyphosis in the dorsal region, the normal degree of lumbar lordosis is reduced or accentuated, and the gait is stooping. Motion in the hip, knee and shoulder joints becomes limited and painful. The intensity of symptoms and physical disability varies in different individuals. Of the three patients we have observed two were males in their late fifties, both exhibiting marked arthritis in roentgenograms; one was totally incapacitated, the other able to walk clumsily but without pain. The third patient, a ninety-four year old woman, first experienced joint symptoms and difficulty in getting about when she was well into her eighties.

On roentgenographic examination the presence of thin, densely calcified intervertebral discs is characteristic. (Fig. 6.) They become frayed and in some instances are extruded or resorbed and adjoining vertebral bodies become fused. In addition, degenerative osteo-arthritic changes are apparent in the spine and lumbosacral, sacroiliac, shoulder, hip and knee joints.

Calcific deposits are commonly seen in muscle tendons about the large joints. It is interesting that the smaller joints exhibit little or no alteration.

Although much is known about the clinical course of alcaptonuria, the specific nature of the metabolic derangement has not been established. There has been much discussion as to whether homogentisic acid normally occurs during the catabolism of tyrosine and phenylalanine or whether it represents an aberrant pathway present only in alcaptonurics. The consensus is that homogentisic acid occurs normally but that there is also an alternate route which is followed by only a small proportion of tyrosine and phenylalanine.[9,10]

It has been demonstrated that alcaptonurics are unable to metabolize compounds with hydroxyl groups attached to the 2,5-positions of the benzene ring. Homogentisic acid has such a configuration. (Fig. 4.) Since a definite hereditary incidence has been established in alcaptonuria, it seems logical to infer that a defect in some enzyme system essential for the breakdown of this chemical configuration is transmitted. It was suggested many years ago that this enzyme might be tyrosinase, even though its presence in man has not been demonstrated. In 1939 and 1940 we injected large doses of a preparation of tyrosinase subcutaneously into one patient without altering the rate of excretion of homogentisic acid. Other substances which might conceivably participate in enzyme systems were administered in large doses individually and in many instances additively while the patients were on a diet of constant composition. These included the synthetic vitamins of the "B" complex which were available at that time (nicotinic acid, thiamin chloride, riboflavin, pyridoxine and calcium pantothenate), ascorbic acid and the fat-soluble vitamins (A, D and K).[11] In addition, brewers' yeast, crude and purified liver extracts and as much as 25 units of regular insulin a day (10-5-10) and 20 cc. of adrenal cortical extract were administered. Only after brewers' yeast was a change in homogentisic acid excretion noted, and this was an increase presumably because of the high protein content of the yeast. To date the only established method of altering the daily output of homogentisic acid is by varying the protein intake. This, no doubt, is equivalent to varying the tyrosine and phenylalanine content of the diet.

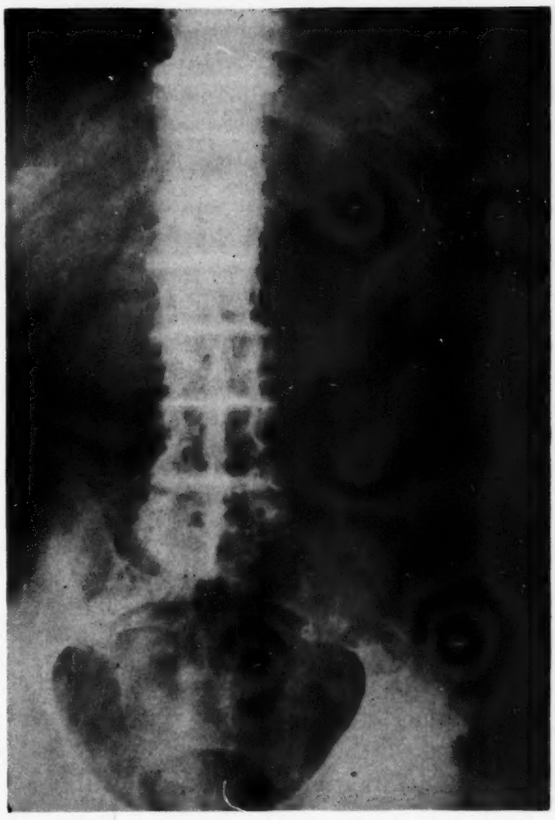

FIG. 6. X-ray of spine in alcaptonuria showing densely calcified intervertebral discs, with osteoarthritis of spine.

Prior to our studies a comparison of the rate of excretion of homogentisic acid in two or more alcaptonurics who were on the same diet had not been made. It seemed worth while to carry out such observations in both our patients particularly since they were of approximately the same age, height and weight. They were maintained on a diet containing 200 gm. of carbohydrate, 80 gm. fat and, during periods of two to

[9] NEUBERGER, A., KIMINGTON, C. and WILSON, J. M. G. *Biochem, J.*, 41: 438, 1947.

[10] GARROD, A. E. Inborn Errors of Metabolism. 2nd ed. London, 1923, Henry Frowde and Hodder & Stoughton.

[11] STEELE, J. M., DOBRINER, K. and GALDSTON, M. *J. Clin. Investigation*, 19: 792, 1940.

three weeks each, the protein content was increased from 30 to 65, 90 and 130 gm. The average daily excretion of homogentisic acid for each individual during each period was virtually the same: 1.5 gm., 3.5 gm., 5.0 gm., and 7.8 gm. It is apparent that the rate of homogentisic acid output varied with the protein content of the diet and that the metabolic disturbance was of the same degree in both patients. This is consistent with the view that the metabolic deficiency is complete in all alcaptonurics.

Previous studies revealed that alcaptonurics convert pure tyrosine and phenylalanine to homogentisic acid more rapidly when they are administered in divided doses and that the naturally occurring levorotatory amino acids usually yield more than the racemic mixtures. In our studies a more exact comparison of the conversion of these isomers to homogentisic acid was made possible by intravenous administration of four one-gram doses of L-phenylalanine at hourly intervals to both patients. On another occasion a similar study was carried out with D-phenylalanine. Both patients converted nearly all of the L-phenylalanine (92 per cent) and between 20 and 40 per cent of the D-phenylalanine to homogentisic acid. Approximately 40 per cent of D-phenylalanine was excreted as amino acid, the nature of which was not established. The remainder was not accounted for. It is of interest that all of the L-phenylalanine could be accounted for as homogentisic acid within four hours after the last injection. On the other hand, the conversion of D-phenylalanine was much slower, requiring up to twenty-four hours. Of 10 gm. of L-tyrosine administered by mouth in a single dose along with 4 gm. of ascorbic acid in divided doses, 88 per cent was excreted as homogentisic acid.[12] These studies indicate that the difference between the rate of conversion of L-phenylalanine and L-tyrosine and that of racemic mixtures of these amino acids to homogentisic acid is due to incomplete conversion of the D-component of the racemic form.

[12] SEALOCK, R. R., GALDSTON, M. and STEELE, J. M. *Proc. Soc. Exper. Biol. & Med.*, 44: 580, 1940.

DR. TAGGART: It may be recalled that Garrod emphasized the relatively benign character of the earliest recognized inborn errors of metabolism. That such is not always the case is well borne out by the condition known as galactemia or congenital galactosemia, an inborn error which has been studied particularly by Dr. Howard Mason of our Department of Pediatrics.

DR. HOWARD H. MASON: During the past fifteen years five patients with difficulty in metabolizing galactose have been admitted to the Babies Hospital. All presented similar histories and physical findings. From birth they had had trouble with their feedings if the latter contained galactose, a natural constituent of milk and lactose. They fussed over their bottles, often refused part, appeared to be uncomfortable and frequently vomited. So long as they were kept on a diet which included galactose they did not gain and grow at the normal rate; they were all underweight. The only other regular finding was a prominent abdomen caused by a very large liver. Those who were several months of age when first seen had cataracts.

Urine passed after a meal that included lactose always contained a reducing substance which did not ferment with yeast and gave the other reactions characteristic of galactose. Urine passed after a fast of several hours did not contain this reducing substance. The urine also contained a trace of albumin. Some of the patients showed a positive cephalin-flocculation test.

When all galactose was removed from the diet, sugar disappeared from the urine in a few hours and the albumin in a few days. Shortly thereafter the infants began to gain satisfactorily and gradually the liver receded to normal size.

The concentration of the fasting blood sugar was always within normal limits. Tolerance curves after the ingestion of dextrose and levulose were normal but those after lactose and galactose were distinctly abnormal: the rise was too high and

it took at least seven hours to return to the fasting level. We determined the amount of galactose in the blood by first measuring the total reducing substance, then removing dextrose by fermentation and measuring the remaining reducing substance. The difference gave the concentration of galactose plus a small amount of non-fermentable reducing substance normally present in blood.

These patients never excreted all of the galactose ingested. Usually about one-quarter of that taken appeared in the urine during the next seven hours. It did not seem possible that the loss of such a small amount of sugar could be responsible for the profound disturbance of metabolism that these individuals showed. To explore this point the blood sugar was determined at frequent intervals on two days. The diets on the two days were the same, except that on one day it contained no galactose, i.e., no milk or lactose. On the other day 10 gm. of lactose was substituted in each meal for 10 gm. of other carbohydrate. On the first day the blood sugar rose and fell normally. The day when the diet contained lactose (the disaccharide of glucose and galactose) the total blood sugar remained at a much lower level all day and the blood glucose scarcely varied from 60 mg. per 100 cc. throughout the day. At no time from the first lactose-containing meal until several hours after the last meal was the blood clear of galactose. The fluctuations in the height of the total blood sugar were due almost entirely to variations in the concentration of galactose in the blood. This suggests that under the command to store glycogen during absorption of glucose the liver was removing excessive amounts of glucose from the blood but had great difficulty in removing and converting galactose.

The steps involved in the utilization of galactose and its place in the carbohydrate cycle are not known. That more than phosphorylation by hexokinase is necessary is almost certain. It seems reasonable to conclude that these individuals have difficulty in performing one of the as yet obscure enzyme reactions required in the utilization of galactose. That the error is inborn is evident from the fact that it is present from birth and so far as we know never disappears. That the error is outside the main carbohydrate cycle is made certain by the disappearance of all signs and symptoms and the normal behavior of these children when they are not fed any food which contains galactose.[13]

DR. TAGGART: There may be situations in which apparent inborn errors of metabolism manifest themselves not alone by the excessive excretion or deposition of some given compound but rather by the disorganization of a whole galaxy of physiologic functions. Such appears to be the case in Fanconi's syndrome and certain associated renal tubular conditions which Dr. Kermit Pines will describe.

DR. KERMIT L. PINES: The Fanconi syndrome is a rare disorder of the kidney in which widespread clinical manifestations and often death may result from impairment of certain functions of the renal tubule. Owing to the high incidence of consanguinity among the parents of patients with this disease, its familial character and the appearance of the syndrome in early life,[14] the Fanconi syndrome may well represent an inborn error of metabolism. Like those which have been described, it may result from lack of disorganization of certain enzyme activities within the renal tubule.

This disorder is characterized by a failure of the renal tubular mechanisms for the reabsorption of glucose, amino acids and, probably, inorganic phosphate. Thus excessive quantities of these substances appear in the urine despite normal or even reduced plasma levels. Impairment of the tubular mechanism for the acidification of the urine is suggested by the frequent finding of a high urine pH despite the presence of systemic acidosis. Burnett[15] has shown that

[13] MASON, HOWARD H. and TURNER, MARY E. *Am. J. Dis. Child.*, 50: 359, 1935.

[14] MCCUNE, D. J., MASON, H. H. and CLARKE, H. T. *Am. J. Dis. Child.*, 65: 81, 1943.

[15] BURNETT, C. H., BURROWS, B. A. and COMMONS, R. R. *J. Clin. Investigation*, 27: 527, 1948.

this may be associated with decreased tubular reabsorption of bicarbonate.

Investigation of renal function by clearance technics in two patients has revealed a normal or reduced renal plasma flow and a low glomerular filtration rate.[15,16] The filtration rate, however, is maintained at a sufficiently high level so that nitrogen retention does not occur.

The tubular defects have far reaching consequences. The excessive loss of glucose may lead to depletion of the liver glycogen stores and ketosis. Impairment of the renal base-sparing mechanisms may be an important cause of the acidosis. This situation is probably exaggerated by the increased excretion of amino acids and other organic acids. The consequent loss of base leads to acidosis and is associated with the production of a negative calcium balance.

The continued loss of calcium and phosphorus in the urine leads to the appearance of rickets or osteomalacia which may be the major cause of disability and invalidism. In infants these disturbances in acid-base and water equilibria may lead to death. As one might expect, the serum changes in phosphorus, calcium and alkaline phosphatase are those of osteomalacia.

McCune, Mason and Clarke,[14] from whose review I have quoted liberally, emphasize the probable relationship of the Fanconi syndrome to cystinosis and cystinuria, another inborn error. In four of eleven autopsied cases evidence of cystinosis was found. Dent[17] has studied extensively the excretion of amino acids in adults with the Fanconi syndrome, cystinuria and renal glycosuria. Abnormal amino acid excretion was not found in simple renal glycosuria; excessive excretion of sulfur-containing amino acids was not observed in patients with the Fanconi syndrome, and cystinuria was found to be associated with increased excretion of other amino acids as well.

Treatment of the Fanconi syndrome has not been attended by striking success in the past. The regimen suggested by Albright and Reifenstein[18] has much to recommend it. A high phosphorus and calcium intake in conjunction with large doses of vitamin D would be expected to compensate for the phosphorus-calcium deficit. Alkaline sodium salts would help relieve the acidosis and the associated electrolyte imbalance. In addition, a high carbohydrate intake might be of therapeutic value during episodes of ketosis.

DR. TAGGART: Earlier in this conference Dr. Bonner suggested the possibility that a 1:1 relationship may exist between genes and enzymes. The last inborn error to be presented, congenital methemoglobinemia, may serve in part to establish such a relationship. Hemoglobin in its normal functional state contains ferrous iron. The exposure of hemoglobin to nitrite either *in vitro* or *in vivo* results in the formation of a chocolate-brown pigment, methemoglobin, which contains ferric iron and which is no longer capable of functioning in oxygen transport. It has long been recognized that the administration of certain coal tar derivatives, quinolines, etc., can also result in methemoglobinemia. There is, however, some confusion in the literature because of the failure in many instances to differentiate methemoglobin from sulfhemoglobin. This, of course, is not the group of patients with which we are presently concerned. There are now in the literature some twenty-five cases of congenital or idiopathic methemoglobinemia in which the pigment has been identified spectroscopically. In at least fifteen of these methemoglobinemia is known to have been present since birth.

Clinically, the picture of congenital methemoglobinemia follows a fairly constant pattern. The most prominent finding is a peculiar type of cyanosis easily seen in the skin of face, neck, hands, nail-beds and mucous membranes which is usually described as gray or slate blue in tint and which varies little in intensity from year to year. Occasionally there are complaints of

[16] BRADLEY, S. E. Unpublished data.

[17] DENT, C. E. *Biochem. J.*, 41: 240, 1947.

[18] ALBRIGHT, F. and REIFENSTEIN, E. C., JR. The Parathyroid Glands and Metabolic Bone Disease. Baltimore, 1948. Williams and Wilkins.

headache, nervousness, irritability and on exertion some degree of palpitation and dyspnea. The conjunctival vessels are injected and the general appearance is almost indistinguishable from that seen in the severely cyanotic types of congenital heart disease. Cardiac murmurs are unusual and clubbing of the fingers is absent. Probably the most striking feature of the disease is the relative absence of symptoms in the presence of even severe degrees of cyanosis.

Examination of the blood reveals the presence of a chocolate brown pigment which can be identified as methemoglobin spectroscopically by an absorption band at 630 mμ, in concentrations from a few to over 30 per cent of the total pigment. On exposure to oxygen the blood does not assume its usual bright red color. There is frequently polycythemia with a red cell count of 6 million or more, a total hemoglobin above 17 gm. and a moderate reticulocytosis. The bone marrow in one reported case showed only a normoblastic hyperplasia consistent with polycythemia.

As to hereditary factors, there is no known instance in which congenital methemoglobinemia has occurred in successive generations but its occurrence in two or more siblings has been reported on several occasions. Most notable is the Irish family examined by Gibson in which five of eight children were cyanotic from birth. Blood samples from the five contained methemoglobin in amounts ranging from 11 to 27 per cent of the total hemoglobin. It is of interest that this family was located in a remote mountain village in which considerable interbreeding had occurred over a span of several generations.

The origin of methemoglobin raises an important question. Van Slyke and his associates have found that approximately 0.4 per cent of the pigment in normal human erythrocytes is methemoglobin. It is quite probable that all individuals continually form this abnormal pigment but that this process is counterbalanced by metabolic reactions capable of reducing methemoglobin to the normal ferrous compound. Methemoglobin induced in normal erythrocytes by the addition of nitrite to shed blood is rapidly reconverted to hemoglobin on standing. In 1930 Warburg showed that the reduction of methemoglobin in intact cells is accompanied by the breakdown of glucose to pyruvate and, furthermore, that iodoacetate is capable of interrupting this process. Washed red cells failed to reduce methemoglobin until glucose was added to the suspending medium. All of these findings indicate the participation of glycolysis in the reduction of methemoglobin. The red cells of congenital methemoglobinemics are incapable of reducing methemoglobin, either natural or induced, despite a normal rate of glycolysis. They lack this capacity even when suspended in normal plasma. Conversely, normal red cells retain their ability to reduce methemoglobin when suspended in the plasma obtained from an individual with congenital methemoglobinemia. Consequently, we may conclude that the defect is confined to the red cell.

The recent studies of Gibson appear to afford a reasonable definition of the biochemical defect which underlies congenital methemoglobinemia. The reduction of methemoglobin to hemoglobin involves the addition of an electron. If an atom of hydrogen serves as the electron donor, the reduction of ferric to ferrous iron is accompanied by the formation of an H ion. Or further, if lactate serves as the donor, we may expect that for each two hydrogens removed from lactate during its oxidation to pyruvate two molecules of methemoglobin should be reduced to hemoglobin. This last balanced reaction is one which Gibson[19] has found to hold true in his *in vitro* studies with normal cells. The enzyme system which catalyzes the oxidation of lactate to pyruvate, lactic dehydrogenase, is known to have diphosphopyridine nucleotide (coenzyme I) as its prosthetic group. Consequently, coenzyme I is the first hydrogen acceptor. One may then ask whether reduced coenzyme I is capable of

[19] Gibson, Q. H. *Biochem. J.*, 42: 13, 1948.

reacting with methemoglobin to form hemoglobin? This reaction has been examined and found to occur at a very limited rate. The gap in electron transport between reduced coenzyme I and methemoglobin is bridged by yet another enzyme, a flavoprotein known as diaphorase. The flavin prosthetic group of this enzyme is capable of accepting 2H from reduced coenzyme I and in turn donating the electrons to 2 molecules of methemoglobin. We may then reconstruct the pathway of electron transport as follows: lactate → coenzyme I → flavin → methemoglobin. Time does not permit a detailed description of Gibson's many and interesting experiments on the blood cells of normal and methemoglobinemic individuals. In brief, he has found that the defective cells differ from the normal in only one important respect. In each of the blood samples which he has obtained from five cases of congenital methemoglobinemia there has been a striking deficiency of the flavoprotein diaphorase. As a consequence the chain of reactions linking the oxidation of lactate with the reduction of methemoglobin is interrupted. It should be pointed out that lactate oxidation is probably only one of several oxidation reactions which may be linked with methemoglobin reduction through the same flavoprotein enzyme. Thus it appears quite tenable that a single enzyme defect may underlie as profound a disturbance as congenital methemoglobinemia. If we make the reasonable assumption that the loss of a single gene is responsible for this defect, it is indeed conceivable that this inborn error exemplifies the 1:1 relationship between genes and enzymes of which Dr. Bonner spoke.

The severity of congenital methemoglobinemia can be strikingly modified by the continued oral administration of either ascorbic acid or methylene blue. The mechanisms by which these agents decrease the amounts of circulating methemoglobin to low values and thereby restore the oxygen capacity of the blood are not entirely clear. It appears likely that ascorbic acid acts directly as a reducing agent on methemoglobin. The dehydroascorbic acid formed may in turn be reduced by glutathione and re-enter the cycle. The action of methylene blue is more obscure. Gibson believes that methylene blue opens up new pathways of electron transport between certain coenzyme II dehydrogenases and methemoglobin. We may take as the starting point, for example, the dehydrogenation of hexosemonophosphate to phosphogluconate. The pathway utilized in the reduction of methemoglobin would then involve the following intermediate carriers: coenzyme II, a diaphorase specific for reduced coenzyme II, and methylene blue. According to Gibson's view, such coenzyme II systems play an insignificant role in the normal reduction of methemoglobin, probably because the specific diaphorase does not react directly with methemoglobin. The introduction of methylene blue bridges this gap and completes the coupling between the oxidation of hexosephosphate and the reduction of methemoglobin.

At the beginning of this clinic mention was made of the fact that Garrod recognized only four metabolic disturbances as distinct inborn errors. As you are well aware, the list has lengthened greatly during the past forty years. Suffice it to say that inborn errors have been encountered in every major division of metabolism. We have in addition to those already mentioned, fructosuria, galactosuria, von Gierke's disease, phenylpyruvic oligophrenia, tyrosinosis, the lipoidoses of Hand-Schüller-Christian, Gaucher and Tay-Sachs, porphyria, familial periodic paralysis, fragilitas ossium and others too numerous to list. When one considers the variety and number of chemical reactions which occur in every living cell, it is not surprising that variants in one respect or another should be encountered with considerable frequency. The fact that the list of recognised inborn errors of metabolism has grown so many-fold during the past forty years should lead us to expect many more as yet unrecognized. The detection of new types of inborn errors may be expected to contribute information concerning areas of intermediary metabolism which remain obscure at the present time.

More importantly, they may broaden our understanding of the manner in which genetic factors determine the chemical constitution of living cells. For the students I should add that the uncovering of new inborn errors will require a lively curiosity, willingness to do a little unusual laboratory work on occasion and above all, obtaining a good family history.

SUMMARY

DR. FREDERICK K. HEATH: Inborn errors of metabolism may be considered to be the result of an alteration in a specific biochemical reaction or series of reactions. In the case of the mold Neurospora, it has been demonstrated that single genes may control individual biochemical reactions through specific enzymes; that this tendency to control is dominant; and that through gene mutation a recessive altered enzyme specificity may be transmitted under suitable genetic conditions, becoming apparent as an abnormal nutritional requirement.

If this information be applied to man, estimated to have tens of thousands of distinct genes, it becomes probable that many inborn errors of metabolism remain to be recognized. Furthermore, a reasonable basis is given for certain features of these disorders, e.g., their relative infrequency, their familial character often associated with consanguinity and their appearance in early life.

Although many diseases have been classified as belonging to the group of inborn errors, this clinic considered only four of the better understood examples. Alcaptonuria, characterized by the excretion of homogentisic acid in the urine proportional to the protein intake, is regarded as resulting from a defect in the metabolism of 2,5-hydroxybenzene compounds, particularly phenylalanine and tyrosine. Such urine when acid is normal in color but on standing turns black at the air surface or becomes brown or black when alkaline; it reduces Benedict's solution and turns blue with ferric chloride. Individuals so affected develop ochronosis in later life due to the deposition in fibrous tissues, cartilage and atheromas of a black pigment thought to be a polymer of homogentisic acid. Hence gray, brown or blue pigmentation may be noted in skin and sclerae, and in the aural, nasal and joint cartilages. Osteoarthritis of the intervertebral and larger joints is common. No therapy is known.

Congenital galactosemia becomes manifest in infants, who exhibit vomiting, failure to grow or gain weight, hepatomegaly sometimes with positive cephalin-flocculation tests, cataracts, a [illegible] albumin in their urine. On a galactose-free diet all manifestations of the disorder disappear. The nature of the defect responsible for the inability to metabolize galactose is unknown.

The Fanconi syndrome is presented as a renal tubular defect characterized by impairment in the reabsorption of glucose, amino acids, inorganic phosphate and possible bicarbonate. The urine tends to be alkaline. Depletion of liver glycogen follows from the loss of urinary glucose. Acidosis, to which the ketosis, amino acid excretion and loss of base all contribute, leads to a negative calcium balance. Replacement therapy is advised.

In congenital methemoglobinemia a specific red blood cell enzyme defect in diaphorase, a flavoprotein, has been described which may be responsible for the failure of these individuals to reduce naturally occurring methemoglobin to the ferrous form. Ascorbic acid directly and methylene blue indirectly may aid in this reduction and so modify the severity of the disease.

The clinic thus emphasizes the role of genetic factors in determining the enzymic constitution of cells and thereby the metabolic behavior of the whole organism, whether mold or man. It also brings out the need of modification of Garrod's original concept of the relatively benign and non-progressive character of inborn errors of metabolism, since it is now clear that accumulation of even normal metabolic intermediates may have deleterious effects. Finally, the growing significance of the clinical implications of our expanding knowledge of the role of enzyme systems is brought out.

Clinico-pathologic Conference

Hematuria, Pneumonia and Cachexia*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. H. (No. 161941), a white male seventy-six years of age, entered the Barnes Hospital on July 31, 1948, complaining of indigestion, bloody urine, cough and fever. Because he was obtunded on admission the history had to be secured from his daughter. The family history was irrelevant. The patient had apparently enjoyed good health most of his life; he had worked as a farmer and as a laborer in various factories until he was over seventy years of age. Except for occasional dizzy spells and marked constipation during the five or six years prior to admission the systemic review was not remarkable. One year before admission the patient began to note abdominal discomfort; he complained of distention, belching and nausea but did not vomit. Soon after the onset of these symptoms he also noted a "gnawing sensation" in the upper abdomen which was relieved by the taking of food. No other details were known.

Three months before admission to the hospital the patient was seen in the Washington University Clinics. According to the history recorded there the patient had passed grossly bloody urine on three occasions, six months, three months and one month before coming to the clinic. The urine was said to have been bright red and on one occasion the patient estimated that he voided approximately a pint of blood containing dark red clots. He also had noted brown stains on his underwear which he interpreted as being due to old blood. For several years he had had marked nocturia but no other definite urinary symptoms.

In the clinic physical examination was within normal limits. The liver edge could be felt at the costal margin but was described as being smooth and not tender. Roentgenograms of the gastrointestinal tract were indeterminate. A blood Kahn test was positive and urinalysis revealed a few red cells on microscopic examination. Otherwise the laboratory findings were not remarkable and although the patient was seen both in the medical and surgical clinics no diagnosis was made. In the several months prior to his hospital admission he had progressive anorexia and for the two weeks immediately preceding entry refused all food and was bedridden. About ten days before entry he had a sudden severe pain in the left chest which lasted a few hours and then gradually subsided. Four days prior to entry he developed fever and a cough productive of ½ pint of dark colored sputum. Constant persistent headache was noted. On the day before entry he had a shaking chill. It was stated by his daughter that the patient had exhibited mental confusion over the course of the year prior to entry and during the same period he had lost between 15 and 20 pounds.

At the time of entry to the Barnes Hospital physical examination revealed a temperature of 38.4°C., pulse 110, respirations 24 and blood pressure 110/60. The patient was a gaunt, dehydrated, emaciated old man who was disoriented and somewhat obtunded. He lay flat in bed and coughed frequently; his cough was productive of thick, yellow, tenacious sputum. The skin was dry and loose. The conjunctivae were

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

pale. The pupils reacted to light and accommodation. Examination of the fundi revealed only arteriolar narrowing. There was crusting in the nose. The lips were dry and cracked and the tongue was also dry. The pharynx appeared reddened and was covered with thick secretion. The neck was stiff. The patient resisted attempts by the examiners to move his extremities or to open his mouth, but it was difficult to determine whether his reaction was voluntary or involuntary in origin. The anteroposterior diameter of the thorax was increased and the chest was resonant to percussion except at the right base. Over this area the breath sounds were diminished and many fine, crackling rales were heard. The left border of cardiac dullness extended 10 cm. to the left of the mid-sternal line in the fifth interspace. The heart sounds were distant and there were occasional ventricular premature contractions. A blowing grade II systolic murmur was heard at the apex. The abdomen was scaphoid and in the epigastrium a large firm mass, which moved only slightly with respiration, was felt. It extended from the right mid-costal border to a similar point on the left. Its lower border could not be defined. The prostate was enlarged to twice its normal size but rectal examination was otherwise negative. Aside from the spasticity noted the neurologic examination was not remarkable. There were no pathologic toe signs.

The laboratory data were as follows: Blood count: red cells, 4,260,000; hemoglobin, 12.5 gm.; white cells, 19,950; differential count: juvenile forms, 4 per cent; stab forms, 36 per cent; segmented forms, 52 per cent; lymphocytes, 7 per cent; monocytes, 1 per cent. Urinalysis: entirely negative except for 1 or 2 red blood cells per high power field in the centrifuged sediment. Stool examination: guaiac positive. Cardiolipin test: negative. Sputum: smear, many white blood cells and gram-positive diplococci; mouse inoculation, pneumococci which could not be typed. Blood cultures: negative. Blood chemistry: non-protein nitrogen, 38 mg. per cent; total protein, 5.7 gm. per cent; albumin, 2.9 gm. per cent; globulin, 2.8 gm. per cent. Roentgenograms: The chest film revealed the cardiac silhouette to be normal. There was an area of increased density in the left middle lung field which was thought to be due to overlying soft tissue and not within the lung parenchyma. There was considerable soft, feathery infiltration in the right middle and lower lung fields consistent with pneumonia. Scoliosis of the spine was present. A portion of the eighth rib posteriorly on the left was absent, presumably as a result of previous surgery. Impression: pneumonia, right middle and lower lobes. Electrocardiogram: defective intraventricular conduction approaching S type bundle branch block.

Because of the apparent stiffness of the neck a lumbar puncture was performed shortly after the patient was admitted. Examination of the spinal fluid revealed no abnormalities. When the patient was examined by the attending physician following admission, he noted changes in the abdominal findings previously described; he was unable to feel the mass which had been recorded by the intern and assistant resident who had admitted the patient.

The patient was given penicillin, intravenous fluids and general supportive therapy and by the third hospital day had shown definite clinical improvement; he seemed hydrated and more rational. He continued, however, to refuse food. His temperature ranged between 37° and 38°C. and his pulse averaged 90. In an attempt to achieve adequate nutrition a nasal tube was passed on the seventh day and the patient was given frequent tube feedings. On the twelfth hospital day repeat laboratory studies revealed the red count to be 3,240,000. The white count was 13,850 with a differential showing a pronounced left shift. Examination of the urine revealed 15 to 25 red blood cells per high power field but the nonprotein nitrogen had fallen to 25 mg. per cent. The patient continued to improve until the fifteenth hospital day when once again he was noted to be lethargic. Ex-

amination again revealed rigidity of the neck similar to that noted on admission. A second lumbar puncture was done and again the spinal fluid was found to be entirely normal.

Repeat chest films on the ninth and twelfth days revealed decrease in the pneumonic infiltration in the right middle and lower lobe. Absence of the eighth rib on the left was again noted although no history of an operation could be obtained and no scar was present. The acid phosphatase was 2 King-Armstrong units. An open film of the abdomen revealed no masses. Hypertrophic osteoarthropathy, however, was noted in the lumbar spine and there was calcification of the intervertebral discs. Films of the long bones of the legs revealed evidence of an old healed fracture of the right femur. No Bence-Jones protein was found in the urine.

During the second and third weeks the patient's temperature averaged about 37.5°c. although his pulse was somewhat elevated. Once again he became more alert. On the twenty-first hospital day a special gastric fill-up showed no evidence of intrinsic gastroduodenal disease or disturbance in motility. On the twenty-fourth hospital day the white count was found to be 21,000 with 9 stab forms and 81 segmented forms. The temperature rose to 38.8°c. and he began to cough. The sputum culture revealed non-hemolytic staphylococcus albus, B. proteus and non-hemolytic streptococci. Streptomycin therapy was begun at this time.

Physical examination again showed the neck to be stiff. There was questionable dullness with suppression of breath sounds at the right base and axilla. The abdomen was soft but no masses were noted. On the twenty-fifth hospital day, August 23, 1948, the patient suddenly collapsed and died.

CLINICAL DISCUSSION

Dr. W. Barry Wood, Jr.: This case presents a difficult diagnostic problem. Because the patient was so seriously ill when he entered the hospital some of the procedures which might have led to the definitive diagnosis could not be carried out. It is clear that the patient had pneumonia but it likewise is apparent that he was also afflicted with a serious, chronic disease. As supportive evidence for the latter statement, I should like to read you the description of the patient written by the assistant resident physician who admitted him to the ward. His description was as follows: "The patient is a gaunt, cachectic, pale, dehydrated, delirious, almost moribund, very old man, constantly mumbling incoherent and unintelligible sounds. He is negativistic, lying comfortably flat abed without dyspnea. The neck veins are very easily seen, distended only to the horizontal level of the clavicle. His breath has a sour, doughy odor which I associate with gastric carcinoma. All of the subcutaneous fat and much of the body muscle have been wasted away." Certainly the writer of that note was considering the diagnosis of carcinoma in addition to that of pneumonia. Finally, the absence of a part of the eighth rib suggests the possibility of a metastasis. Dr. Grunow, would you comment on this point?

Dr. Otto H. W. Grunow: Our first thought when we saw the chest film was that the patient probably had had surgery involving the eighth rib; this explanation was ruled out by the history and physical examination. Usually when a portion of a rib has been removed surgically, remains of the periosteum can be seen. The findings in this case thus suggested to us the possibility of metastatic tumor which had replaced the rib.

Dr. Wood: If we assume for the moment that this patient may have had metastatic involvement of his rib, we may consider possible primary sites. Dr. Taussig, do you have any suggestions in this regard?

Dr. Barrett L. Taussig: This patient had gross hematuria on several occasions before hospital admission, and microscopic hematuria was noted during his hospital stay. Carcinoma of the kidney not infrequently metastasizes to the lung and I should like to suggest it as a possibility.

DR. WOOD: That possibility is certainly one which must be considered. Dr. Goldman, do you care to add another diagnosis?

DR. ALFRED GOLDMAN: In view of the history of gastrointestinal complaints one must consider carcinoma of the gastrointestinal tract.

DR. WOOD: Can you localize the site within the gastrointestinal tract? You will recall that the gastric fill-up which was begun while the patient was in the hospital was negative and a gastrointestinal series done in the clinic was likewise negative.

DR. GOLDMAN: Those examinations do not rule out either carcinoma of the stomach or of the esophagus.

DR. WOOD: Dr. Scheff, do you take exception to that statement?

DR. HAROLD SCHEFF: Our experience here indicates that the x-ray examination will lead to a correct diagnosis in about 95 per cent of cases. This man had two upper gastrointestinal examinations by x-ray, both negative, and therefore I would think that it is very unlikely that he had carcinoma either of the esophagus or of the stomach.

DR. GOLDMAN: I agree that in a great majority of instances the x-ray department is able to make the correct diagnosis in gastrointestinal malignancy, but we have all seen occasional proved cases in which the x-ray studies were negative.

DR. WOOD: Dr. Kenamore, do you have any further information on this subject:

DR. BRUCE D. KENAMORE: The percentage of correct diagnoses of gastrointestinal carcinomas by x-ray examination varies from institution to institution. This department has an excellent record; figures from the Mayo Clinic are comparable to those collected here.

DR. WOOD: Dr. Scott, is there any other site of intra-abdominal carcinoma which should be mentioned?

DR. VIRGIL C. SCOTT: I believe carcinoma of the pancreas should be included.

DR. WOOD: If one considers again the possibility that this man had a metastatic tumor in the rib, what primary site would one think of?

DR. SCOTT: Carcinomas arising in the breast, prostate, thyroid and stomach frequently metastasize to bone.

DR. WOOD: Should not carcinoma of the lung be considered in this regard? The patient had signs of pulmonary infection; the process was only temporarily controlled by antibiotic therapy. It seems to me that this patient may have had carcinoma of the bronchus with pneumonia secondary to obstruction.

DR. GOLDMAN: That possibility seems unlikely to me.

DR. CARL V. MOORE: Is there any further description in regard to the epigastric mass described in the protocol?

DR. WOOD: I have looked through the hospital record, Dr. Moore, and can give you the following information. On the day of admission, as was noted, the mass was felt by both the intern and assistant resident. When Dr. Paul Hagemann, who was attending on the ward, saw the patient on the second hospital day he could feel no mass. Early that morning the patient had had a bowel movement and from that time on no one felt the mass. The possibility, therefore, that it was fecal material must be considered. However, the description by the admitting assistant resident was quite convincing.

DR. EDWARD H. REINHARD: One does not usually feel fecal material within the bowel in the epigastrium.

DR. WOOD: Furthermore, the barium enema revealed that the patient's transverse colon was rather redundant and lay well below the umbilicus. Consequently, fecal material within the colon probably could not have been felt in the epigastrium. The fact remains, however, that no one felt the mass after the patient's first day in the hospital. Dr. Hagemann, can you comment further on this point?

DR. PAUL O. HAGEMANN: I recall the patient very well. He held his abdomen rather tensely and it was difficult to palpate as thoroughly as one would have liked.

DR. WOOD: There are notes, however, Dr. Hagemann, in the chart by several of the house officers who recorded the fact that on occasions when the patient was relaxed and palpation of the abdomen was satisfactory no mass could be felt. I do not think we can reach a definite conclusion on this point. Are there any other suggestions in regard to diagnosis?

DR. C. V. MOORE: I think that carcinoma of the kidney and carcinoma of the stomach are the most likely possibilities; but if the patient had indeed had an epigastric mass, one would have to include retroperitoneal lymphoma in the differential diagnosis: it may involve the ribs, the lungs and the kidneys although involvement of all three concomitantly would be unusual.

DR. WOOD: Should multiple myeloma not be considered?

DR. C. V. MOORE: I think it is not particularly likely but it is a possibility. There was no mention of auto-agglutination of the red cells and the patient did not have Bence-Jones proteinuria. The serum globulin was not particularly high. A bone marrow examination would have been helpful in establishing or ruling out that diagnosis. Was a skull film obtained?

DR. WOOD: No skull film was taken.

DR. EDWARD MASSIE: Would you consider tuberculosis as a remote possibility?

DR. GOLDMAN: I would think malignant disease is much more likely. The pulmonary lesion did not resemble that usually seen in tuberculosis and I do not think the clinical course was consistent with it.

DR. ROBERT J. GLASER: Did this patient have any subsequent stool examination for occult blood?

DR. WOOD: There was only one recorded.

DR. GLASER: A month or so ago we saw a similar patient whose findings were primarily pulmonary but who at autopsy was found to have a carcinoma of the stomach with metastases to the lung.

DR. LEO J. WADE: Dr. Wood, should not carcinoma of the prostate be considered?

DR. WOOD: The fact that the acid phosphatase was normal makes carcinoma of the prostate with metastases quite unlikely. Dr. Taussig, what further evidence can you muster in support of the diagnosis of carcinoma of the kidney?

DR. TAUSSIG: The patient's first symptoms were apparently gastrointestinal in origin but they were rather indefinite. The first definite evidence of disease was the appearance of obvious hematuria six months before he came to the clinic. When one considers the causes of hematuria, he includes chiefly renal stone, tuberculosis and carcinoma. In a man who is seventy-six years of age and who has been well all of his life it seems to me that carcinoma would be the foremost possibility.

DR. WOOD: If he did not have carcinoma of the kidney, the hematuria would have to have been incidental. Dr. Goldman, do you believe that the patient's pulmonary lesion may be due to metastases?

DR. GOLDMAN: It is impossible to say. We have seen many patients whose x-ray findings were not suggestive of carcinoma, either primary or metastatic, who at autopsy had malignancy.

DR. WOOD: Could renal cell carcinoma produce an osteolytic metastasis and thus explain the absence of a portion of the eighth rib?

DR. C. V. MOORE: Yes, I think that is entirely possible.

DR. WOOD: The evidence which we have just received makes a fairly strong argument for the diagnosis of carcinoma of the kidney. Dr. Hagemann, do you agree that it is the most likely diagnosis?

DR. HAGEMANN: Yes, I do. I think in retrospect the hematuria should certainly have been investigated further, particularly when he came to the clinic. By the time he was admitted to the ward his condition was such that extensive investigation could not be carried out.

STUDENT: It is said that blood which originates as a result of bleeding from the kidney itself is less likely to produce clots than bleeding from a lesion in the bladder. Does that point influence you, Dr. Taussig?

DR. TAUSSIG: No, I do not think so.

DR. C. V. MOORE: I think that statement is correct in general but certainly there are exceptions.

DR. ROBERT A. MOORE: I have heard urologists make that statement on a number of occasions but I have seen clots in the ureter give rise to the signs of renal colic.

DR. GLASER: I agree that this patient probably had carcinoma of the kidney, but I do not believe that carcinoma of the stomach can be ruled out in view of the guaiac positive stool. Unfortunately, we have only one determination. Had the finding been substantiated on several occasions I would think it very likely that the patient had two carcinomas—one of the kidney and one of the stomach. Multiple carcinomas, although not as common as single ones, occur more frequently than is often realized. I would find it difficult to explain the guaiac positive stool on the basis of carcinoma of the kidney.

DR. WOOD: The guaiac reaction was only 1+ on the single examination.

DR. GLASER: The case to which I referred previously likewise only had a 1+ guaiac stool.

DR. WOOD: Do you believe that carcinoma of the stomach is more likely than carcinoma of the kidney?

DR. GLASER: No, but I certainly think it has to be considered.

DR. LLEWELLYN SALE, JR.: I do not think that carcinoma of the prostate with metastases can be ruled out on the basis of one determination of the acid phosphatase.

DR. WOOD: The examination of the prostate did not suggest carcinoma to any of the examiners.

DR. KENAMORE: Carcinoma of the urinary bladder should be mentioned in passing. I think the intermittent bleeding suggests it.

DR. WOOD: Dr. Moore, does carcinoma of the bladder frequently metastasize to the ribs?

DR. R. A. MOORE: It is quite uncommon but, of course, anything is possible where carcinoma is concerned.

STUDENT: Carcinoma of the thyroid frequently metastasizes to bone; presumably, this patient, however, did not have anything to suggest primary involvement of the thyroid gland.

DR. WOOD: There is one other point which I should like to take up. This patient apparently had pneumonia at the time of his death. When he entered he had signs of pneumonia and following adequate penicillin therapy made a satisfactory response; apparently he then suffered a relapse. Dr. Hunter, what explanation do you offer for this sequence of events?

DR. THOMAS H. HUNTER: There may well have been a change in the bacterial flora in the involved lung. It now seems quite clear that in patients with pneumonia, particularly those terminally ill with some other disease, penicillin-sensitive organisms may be eliminated only to allow gram-negative rods to become predominant. Such a second infection may prove fatal; we have seen a number of such instances.

DR. WOOD: In a recent staff conference here that point was discussed. Probably the patient's terminal bacterial pneumonia was due to penicillin-fast organisms. Streptomycin was given only on the very last day and probably could not have exhibited an effect even were the organisms sensitive to it. We hope that Dr. Moore will be able to show us bacterial stains of the lung in order to clarify this point.

DR. WOOD: In summary, I believe that it is the general concensus that this patient had malignant disease, the primary site most likely in the kidney. A number of alternative possibilities such as carcinoma of the stomach, of the prostate, of the lung and of the pancreas have been mentioned. Terminally, pneumonia, probably due to gram-negative rods was present.

DR. REINHARD: Dr. Wood, what is your diagnosis?

DR. WOOD: I would agree with the staff in putting carcinoma of the kidney first.

Clinical Diagnosis: Carcinoma of the kidney, with metastasis to the eighth left rib; ? carcinoma of the stomach, pancreas, lung or prostate; terminal pneumonia due to gram-negative organisms.

PATHOLOGIC DISCUSSION

DR. THOMAS YOUNG: The left kidney was irregularly enlarged, weighing 330 gm. As the perirenal fat was stripped away from this kidney, dense fibrous tissue was noted which surrounded the lower pole and extended into the hilum. From this region a yellowish orange, fairly well circumscribed mass 4 cm. in diameter bulged from the parenchyma of the lower pole of the kidney. This tumor had a variegated, trabeculated appearance and was predominantly yellow and orange in color. It originated from the parenchyma of the lower pole and extended both centrally toward the pelvis and peripherally toward the cortex. There were linear groups of satellite neoplasms from 1 to 8 mm. in diameter which extended from the central mass to the middle and upper poles, particularly in the cortex. Extending from the pelvis and involving the ureter about 4 cm. below the ureteropelvic junction, a grayish nodular mass partially occluded the lumen of the ureter. The calyces not involved with tumor were dilated and the surrounding parenchyma thinned. A few petechiae were present in the pelvic mucosa. The ureter below the site of the metastatic tumor and the bladder were uninvolved with tumor. The left renal vein was distended and completely occluded by a densely adherent grayish white firm thrombus which extended into the vena cava.

The right kidney contained some nodules of metastatic tumor but no other significant lesions.

The lower lobe of the left lung was bound posteriorly and laterally to the chest wall by dense fibrous adhesions. Less dense adhesions also involved the upper lobe, including the apex. Posteriorly beneath the dense adhesions a large soft yellowish gray mass completely replaced 7 cm. of the eighth rib. On the right, fibrous adhesions were as extensive but not as dense as on the left. Only 20 cc. of serous fluid were present in each pleural cavity. When the thoracic organs were removed, other nodules of tumor, 15 mm. in diameter, were noted in the sixth and ninth right ribs posteriorly. Numerous small scattered subpleural nodules varying from 1 to 8 mm. in diameter were evident over the lungs. On section these nodules of tumor were soft and quite discrete.

Both upper lobes of the lungs were emphysematous, but the lower lobes were heavy and dark red and exuded a frothy, colorless fluid on pressure. In the right apex there was a fibrocalcified scar. In the pulmonary artery a laminated, non-adherent grayish-white firm thrombus partially occluded the vessel. There were smaller thrombi in the tertiary radicles of the artery throughout the lung. No other significant pathologic changes were present in the viscera, and the exterior of the body was notable only for severel decubiti over the sacrum and greater trochanters.

DR. ROBERT A. MOORE: The gross lesions were typical of primary carcinoma of the kidney. The fact that there was tumor invading and filling the renal vein supports the diagnosis inasmuch as it would be very unusual for a metastatic tumor of the kidney to involve the renal vein in that manner. There was no other evidence of a primary tumor in the body. The ten or so nodules in the lung were typical metastatic tumors, and the lesion in the eighth rib had the characteristic appearance of a metastasis; it did not look grossly like any of the tumors, such as chondrosarcoma or osteogenic sarcoma, which might originate in that region. The only problem in this case from the standpoint of histopathology was to confirm the gross diagnosis which was highly presumptive in view of the gross appearance of the tumors in the kidney, the lung and the ribs.

Figure 1 is an illustration of a characteristic field of this tumor in which there are two cellular types. In one portion there are cells with prominent cell walls, relatively clear cytoplasm, and prominent hyperchromatic nuclei, while in other parts of the field there are cells which have acidophilic cytoplasm of rather dense character. These are the two cellular types that are

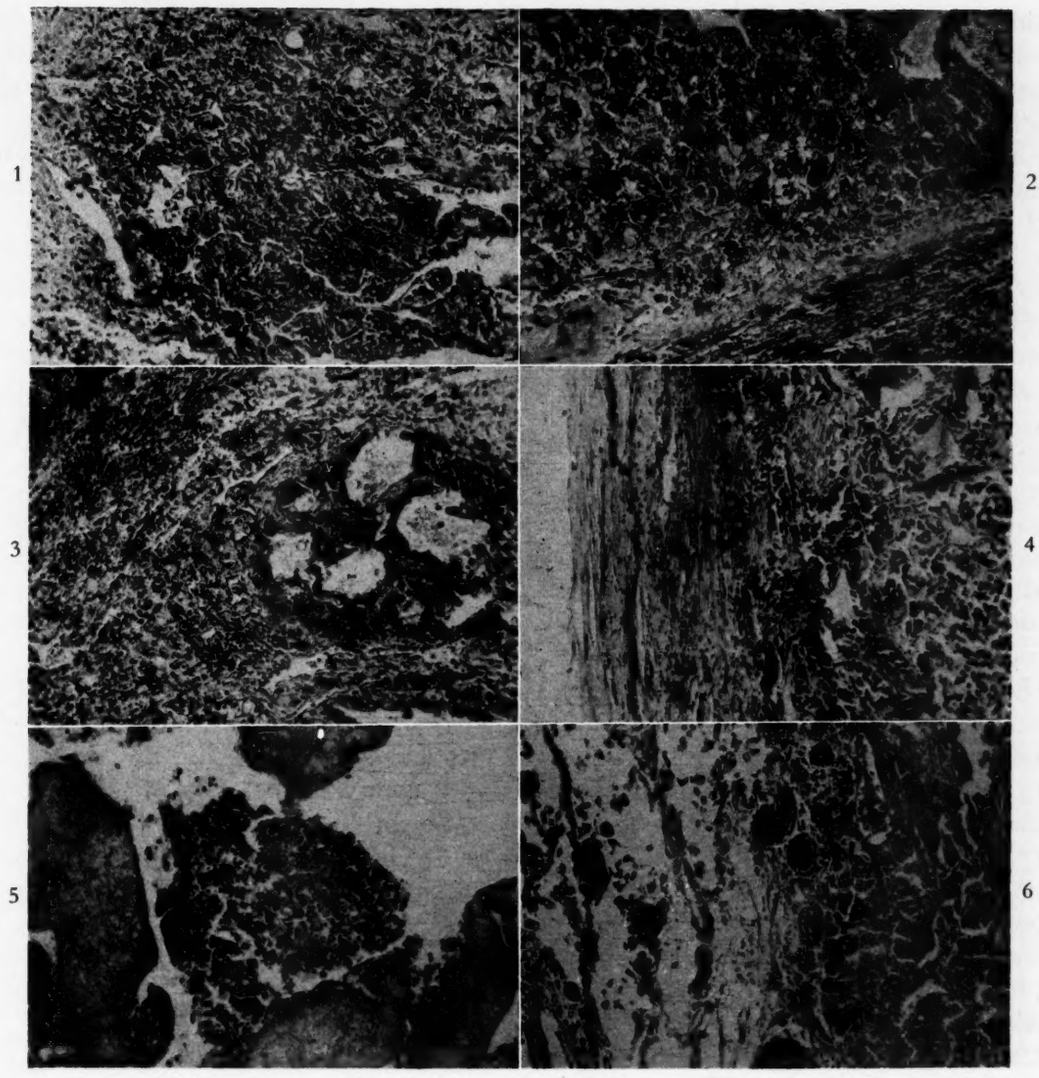

FIG. 1. Renal cell carcinoma of the left kidney with both the clear and dark cell types typical of this tumor.
FIG. 2. Region of highly anaplastic cells in the primary tumor of the left kidney.
FIG. 3. Pseudo-acini in renal cell carcinoma formed by degeneration of the central cells of small masses of tumor.
FIG. 4. Wall of the left renal vein which was occluded by an organized thrombus containing large numbers of invading carcinoma cells.
FIG. 5. Fragment of a thrombus formed in the lumen of the inferior vena cava; recognizable carcinoma cells are contained between masses of degenerated fibrin.
FIG. 6. A section of the edge of a metastatic nodule in the lung with congested alveolar walls on the left and anaplastic carcinoma on the right.

characteristic of renal cell carcinoma. In Figure 2 there is another region of tumor in which there is a distinct anaplasia of the cellular type. Large hyperchromatic cells with bizarre nuclei are seen. These cells are sufficiently undifferentiated that it might be a little difficult to recognize the tumor on the basis of this field alone. In Figure 3 there is a region in which the tumor has a glandular appearance. This section demonstrates very well how the glandular appearance of the renal cell carcinoma originates, at least in some instances, by necrosis of the cells in the centers of small nodules. It is not true glandular formation, for the granular remnants of the necrotic cells lie in the center of the false lumen and the viable peripheral cells have assumed an almost

cuboidal shape. This glandular appearance may be found in almost any renal cell carcinoma if enough sections are cut and enough of the tissue is examined.

In a section of the renal vein (Figure 4) the adventitia and a few of the muscle fibers are seen on the left. In the lumen there is an organized thrombus containing numerous highly anaplastic tumor cells. The renal vein here was tremendously distended with this mass which was composed half of tumor and half of either thrombus or connective tissue of the organized thrombus. Figure 5 is of a small piece of degenerated thrombus which was taken from the lumen of the inferior vena cava at about the level of the diaphragm. It is composed of tumor cells and fragments of degenerating thrombus and presumably originated in the mass in the renal vein. In association with that finding, as Dr. Young has pointed out, there were thrombi in one of the main branches of the pulmonary artery and numerous small thrombi throughout the smaller branches of the pulmonary artery. The emboli in the pulmonary artery probably played at least some role in the rather sudden death of this patient. Figure 6 is an illustration of a section of the lung in which the pulmonary alveolar walls contain congested capillary vessels; on the right there is one of the metastatic nodules which occurred in the lung. These nodules were composed of highly anaplastic tumor cells and occurred both within the alveoli and in the connective tissue of the lung. No evidence of pneumonia was present grossly or in any section.

In summary, this man had a primary carcinoma of the kidney which invaded the renal vein and produced there an occluding thrombus of tumor. There were metastases to three ribs, to both lungs and presumably a terminal pulmonary embolism. The latter was not of the extent usually necessary to produce a fatal outcome, but in this patient who exhibited both dehydration and emaciation, it apparently was the final factor which led to his death. The congestion and edema of the lung in association with the multiple emboli in the small vessels are the only pathologic changes apparently related to most of the pulmonary findings described clinically.

Final Anatomic Diagnoses: Renal cell carcinoma of the left kidney with extension to the renal pelvis and into the left renal vein with complete occlusion of the vein; metastatic carcinoma in the left ureter, all lobes of the lungs, right kidney and eighth left and sixth and ninth right ribs; thrombi in the pulmonary artery; thrombi in small blood vessels of lung; congestion and edema of the lungs.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Renal and Cardiac Lesions in Potassium Deficiency Due to Chronic Diarrhea*

JAMES G. PERKINS, M.D., ARTHUR B. PETERSEN, M.D. *and* JAMES A. RILEY, M.D.
Portland, Oregon

POTASSIUM deficiency has been described in diabetic acidosis,[1–4] Addison's disease during therapy with desoxycorticosterone,[5–7] alkalosis,[8–10] Cushing's syndrome complicated by alkalosis,[11,12] infantile diarrhea,[13,14] chronic renal disease[15] and in the sprue syndrome.[16,17] Hypopotassemia is present in episodes of familial periodic paralysis.[18] Abnormal electrocardiographic patterns characteristic of hypopotassemia have been observed in some of these conditions by a number of authors.[2,4,19–22]

Renal and cardiac lesions have been observed in animals made deficient in potassium by diets adequate in all essentials except potassium or by prolonged administration of desoxycorticosterone acetate.[23–26]

We have recently observed a patient with chronic diarrhea who exhibited signs, symptoms and electrocardiographic changes commonly seen in potassium deficiency. These abnormalities were corrected by the oral and intravenous administration of potassium. After an initial period of improvement the symptoms and signs of hypopotassemia suddenly reappeared during the intravenous administration of glucose and the patient died of respiratory paralysis. Lesions that we believe were due to potassium deficiency were found in the heart and kidneys at necropsy.

CASE REPORT

Mr. L. J. (No. 169851), a forty-six year old white, married chauffeur, was admitted for the second time to the Multnomah Hospital on September 22, 1948, with chronic diarrhea, loss of weight, nausea and anorexia. He was well until 1938 when he noticed transitory attacks of lightheadedness, sinking sensations, nausea and weight loss. Cholecystectomy, appendectomy and inguinal herniorrhaphy at another hospital were accompanied by remission of his symptoms and a gain in weight. The gallbladder showed chronic inflammation and mild cholesterosis.

Five months later, while caring for his father who was ill for two weeks with diarrhea, the patient also developed diarrhea which persisted during the ensuing ten years of his life. At the onset he had fifteen to twenty voluminous, watery or mushy, brown, grey-green or yellow stools daily. These had a very foul, sometimes ammoniacal odor and contained gas bubbles. Defecation was frequently accompanied by explosive flatulence. No pain or fever was experienced and the diarrhea never occurred at night. He was thoroughly studied by several physicians, none of whom demonstrated an organic basis for his illness. Most examiners noted a mild normocytic anemia. In addition to symptomatic treatment he received iron, folic acid, liver extract and pancreatic extract for several months without benefit. Vitamins were given in abundance. Roughage and chemically stimulating foods made the diarrhea worse. A low-carbohydrate, high-protein diet failed to alter the course. Sometimes the daily number of stools dropped to four or five but their character remained abnormal. Since February, 1947, he had experienced recurrent attacks of extreme exhaustion, depression and desire for death which would last for two or three days. During these episodes he would remain in bed, breathing would be difficult and he could speak only with a weak voice. A diminution in the number of stools often terminated these attacks. Until February, 1948, his appetite remained

* From the Departments of Medicine and Pathology of the University of Oregon Medical School, Portland, Ore.

fairly good and his weight fluctuated with the frequency of the diarrhea. At this time he began to have anorexia and nausea and diminished intake of food.

A social and psychiatric investigation disclosed an insecure, dependent individual with insufficient drive and conflict which he had concealed from his examiners. He was bitter about not having been informed before his operation that the gallbladder was to be removed, and he feared that some surgical error had caused the present illness because of the suicide of one of his attending physicians.

The patient was an intelligent but passive individual, appearing apathetic and emaciated. He weighed 110 pounds (normal weight 190 pounds). There was no fever. The pulse was regular, 70 beats per minute, and the respiration was normal. The blood pressure was 80/60. The skin was dry, of poor turgor, and a slight generalized brown pigmentation was evident. The hair was normal in amount and distribution. Spoon-shaped curving of the finger and toe nails and softening of the nail beds were noted. The tongue appeared normal. Only six lower front teeth were present. The abdomen was scaphoid and not tender. A sharp, nontender liver edge was palpable 2 cm. below the right costal margin during inspiration and the total depth of the liver in the mid-clavicular line was 8 cm. Slight induration was present in the right ischiorectal fossa. The tendon reflexes were normal. The remainder of a complete physical examination was normal.

Laboratory examination revealed the following: the hemoglobin was 15.0 Gm. per 100 cc.; erythrocytes were 5,100,000 and leukocytes 5,000 per cu. mm. In the differential count of 100 leukocytes there were 64 segmented neutrophils, 1 segmented basophil, 8 band cells, 26 lymphocytes and 1 monocyte. The sedimentation rate was 1 mm. in forty-five minutes (Westergren). The urine was normal, with an acid reaction and a specific gravity of 1.012. The serologic test for syphilis was negative. The total serum proteins were 6.5 Gm. per cent, serum albumin 4.5 Gm. per cent and serum globulin 2.0 Gm. per cent. An oral dextrose tolerance test using 50 Gm. of dextrose showed a flat curve with a fasting level of 65 mg. per cent, a rise to a peak of 99 mg. per cent in one and one-half hours and a fall to 90 mg. per cent in two hours. A standard intravenous dextrose tolerance test[27] was normal. Histamine gastric analysis resulted in no free HCl and 22 units of total HCl. Many examinations of the stools were negative for the usual pathogenic bacteria, parasites, ova and occult blood. Meat fibers and fat globules were reported twice. The grossly abnormal stools have been described. Serum agglutinins were not demonstrated for paratyphoid and typhoid organisms or for Brucella abortus. Initial sigmoidoscopic examination revealed a finely granular mucosa which bled easily on slight trauma. A later examination disclosed slight mucosal hyperemia but no other abnormality. Roentgen study showed the colon to be normal, the stomach to be very ptotic, with small widely separated rugal folds and reduced peristalsis. In the duodenum there were two small diverticula. The progress meal showed moderate hypomotility of the stomach and small bowel, and segmentation of the column of barium in the ileum with a coarse mucosal pattern. These findings were interpreted as due to disordered motor function. Methylene blue given by mouth appeared in the stool in thirteen hours.

Because of the patient's personality, his psychiatric history and lack of evidence for an organic etiology, a functional basis for his illness was considered most likely. Non-tropical sprue was thought to be unlikely because of the prior lack of response to folic acid and liver extract.

The patient was given a high-caloric bland diet of five daily feedings but his intake averaged only about 1,500 calories per day. He received an adequate intake of vitamins A, B, C and D both orally and parenterally; 1,000 cc. of amigen were given daily by intravenous infusion, and after October 4, 1948, 50 Gm. of glucose were added to each of these. Various compounds were used for symptomatic relief of the diarrhea but he continued to have two to three abnormal stools daily and by October 21, 1948, his weight had fallen to 98 pounds. Dilute HCl after meals was begun on October 26, 1948. On this day he also received three intravenous injections of tetraethylammonium chloride in an attempt to block the extrinsic autonomic control of the bowel. After this he had a mild increase in the volume and frequency of the stools. On October 29, 1948, the patient complained of extreme muscular weakness and fatigue. He exhibited ashen pallor, apathy, depression and a will to die. The heart action was regular, 120 beats per minute, and the blood pressure was 70/0. The tendon reflexes were very weak, estimated a −3,

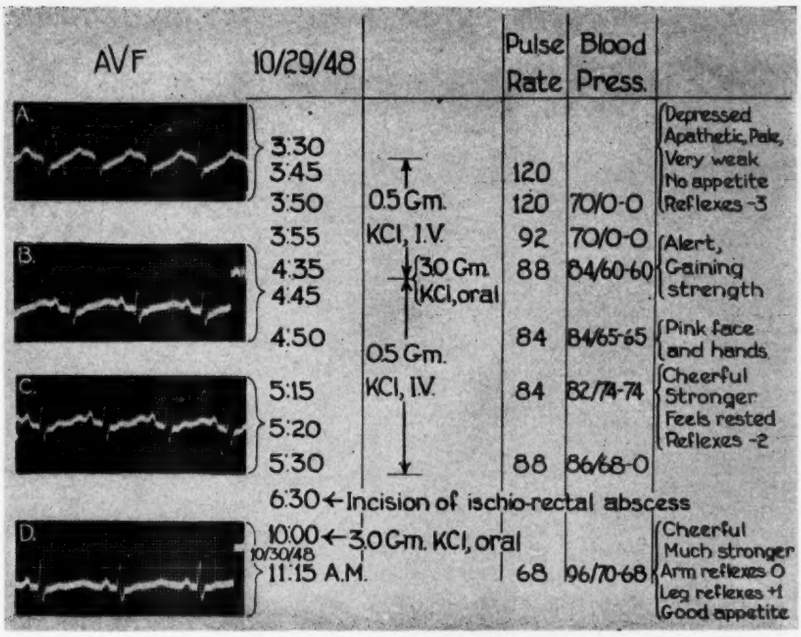

FIG. 1. Correlation of changes in physical findings and in electrocardiographic lead AVF during the administration of KCl; tendon reflexes are estimated on a −4 to +4 scale; 0 is normal.

using a −4 to +4 scale. A fluctuant ischiorectal abscess was present. His temperature was 99.0°F. A blood count showed 16.0 Gm. of hemoglobin per 100 cc., 4,000,000 erythrocytes, 12,250 leukocytes per cu. mm. with 70 per cent segmented neutrophils, 8 per cent band cells, 12 per cent lymphocytes and 1 per cent monocytes. The sedimentation rate was 5 mm. in fifteen minutes and 25 mm. in forty-five minutes. The serum sodium level was 147.8 mEq./L. and the serum potassium 3.75 mEq./L. Standard and unipolar electrocardiograms were taken.

One Gm. of KCl was added to an intravenous infusion, which was adjusted to deliver 0.5 Gm. of this salt per hour. Supplemental oral doses of KCl were given. Figure 1 shows a correlation between the amount of potassium received, the physical findings and serial electrocardiographic tracings. It will be seen that the tachycardia began to subside within ten minutes. This was followed shortly by a rise in blood pressure, disappearance of his depression and a return of alertness, strength and tendon reflexes. The ischiorectal abscess was then opened and packed using a small, low spinal anesthesia. The total intake of KCl was 7 Gm. in six and one-half hours. On the following morning, October 30, 1948, the pulse rate was 68 and the blood pressure 96/70 − 68. His appetite was good for the first time since admission to the hospital.

Serial electrocardiograms taken before, during and after administration of KCl are shown in Figure 2. Tracing A was taken just before administration of KCl. It shows marked depression of the S-T junctions and sagging of the S-T segments in Leads II, III, AVF, and in all of the precordial leads, with reciprocal changes in the S-T junctions and segments in AVR and AVL. AVR and AVL represent potentials from the endocardial aspects of the heart because of its backward rotation on the transverse axis and the S-T junction elevation seen in these leads suggests injury to the endocardial surface of the myocardium.[28] The T waves are flat in Lead I and low positive in those leads facing the epicardial surfaces. The Q-T intervals are prolonged. In the succeeding tracings there is diminution in rate, progressive return of the S-T junctions toward the isoelectric line, and the appearance of more easily recognizable positive T waves. U waves appear in series B and become progressively more prominent. The Q-T intervals in series C are still prolonged, as can be seen in Lead AVL, this being masked in the precordial leads of this series because the T waves are probably diphasic and partially superimposed upon the U waves.

The final tracing, taken thirteen hours after the last dose of KCl, is still abnormal, showing slight depression of the S-T junctions, low T waves, persistent U waves and probably prolonged Q-T intervals.

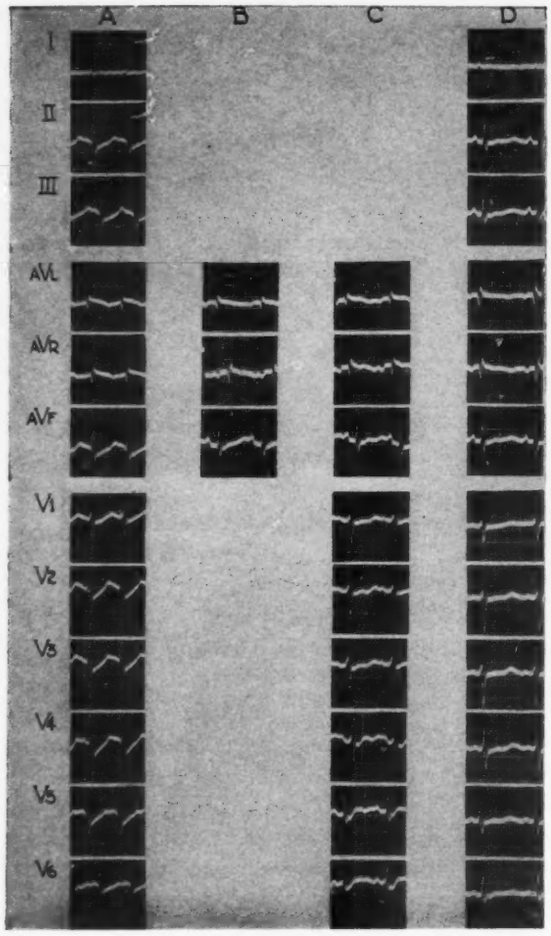

FIG. 2. A, initial record taken while the patient was showing clinical evidence of hypopotassemia; B, seventy-five minutes later after receiving 0.5 gm. of KCl intravenously; C, two hours after A, the patient having received 1.0 gm. of KCl intravenously and 3.0 gm. of KCl by mouth; D, thirteen hours after the last dose of KCl; electrocardiographic abnormalities still persist although the clinical symptoms and signs have disappeared.

On October 30, 1948, the patient ate his breakfast and most of his lunch. At 1:00 P.M. his usual infusion was started containing 2 Gm. of sodium chloride, 50 Gm. of amino acids and 100 Gm. of glucose. This was followed by a flask of 10 per cent glucose in water. He had not yet been given the 3 Gm. oral doses of KCl ordered for him following meals. At 4:45 P.M., after having received 500 cc. of the 10 per cent glucose in water, he became very weak and unable to turn in bed. He rapidly developed tachycardia, extreme muscular weakness with dyspnea and ineffectual struggling to breathe. The tendon reflexes were absent. He died at 5:10 P.M. while emergency treatment was being prepared. Heart blood taken fifteen minutes postmortem yielded a serum potassium concentration of 4.25 mEq./L. The serum sodium level was 146.9 mEq./L. The urine on this day contained one plus albumin.

External examination of the body at necropsy revealed marked emaciation and evidence of dehydration (estimated body weight 85 pounds). No cutaneous lesions, jaundice or areas of hyperpigmentation were encountered. The skin was loose and there was a general loss of tissue turgor. The recent surgical incision in the perineum was free of drainage or apparent infection.

There was a marked loss of fat in the subcutaneous tissues, greater omentum and mesentery. The abdominal viscera appeared unchanged. The mesenteric lymph nodes were moderately enlarged and one of these (1 by 2 cm.) was found to be calcified. Gross examination of the lungs revealed only a moderate passive hyperemia and edema. The heart (weight 250 Gm.) presented no evidence of hypertrophy, dilatation of any of its chambers or other significant changes. The coronary arteries showed only minimal arteriosclerosis.

The liver, spleen, pancreas, esophagus, stomach, small intestine and colon revealed no inflammatory changes or other abnormalities. The gallbladder and appendix were surgically absent.

The adrenal glands were somewhat smaller than expected but otherwise not unusual. The kidneys (combined weight 490 Gm.) were pale and slightly enlarged. The capsules stripped with ease revealing a finely granular subcapsular surface which was free of scarring. On sectioning the kidneys the parenchyma bulged slightly above the capsule; however, the cortex and medulla of each presented a normal ratio and were otherwise not unusual. The remainder of the genitourinary tract showed no abnormal changes. The meninges, brain and pituitary gland presented no pathologic findings.

Microscopically, the liver, pancreas, esophagus, ileum, jejunum, colon, adrenal glands, brain and pituitary revealed no abnormal findings. Both lungs exhibited only a moderate acute passive hyperemia and edema. A mild atrophic gastritis was present as evidenced by lymphocytic and plasma cell infiltration of the submucosa and atrophy of the glands. The spleen and mesenteric lymph nodes disclosed a moderate reticulum hyperplasia but no inflammation or necrosis. The one calcified intra-abdominal

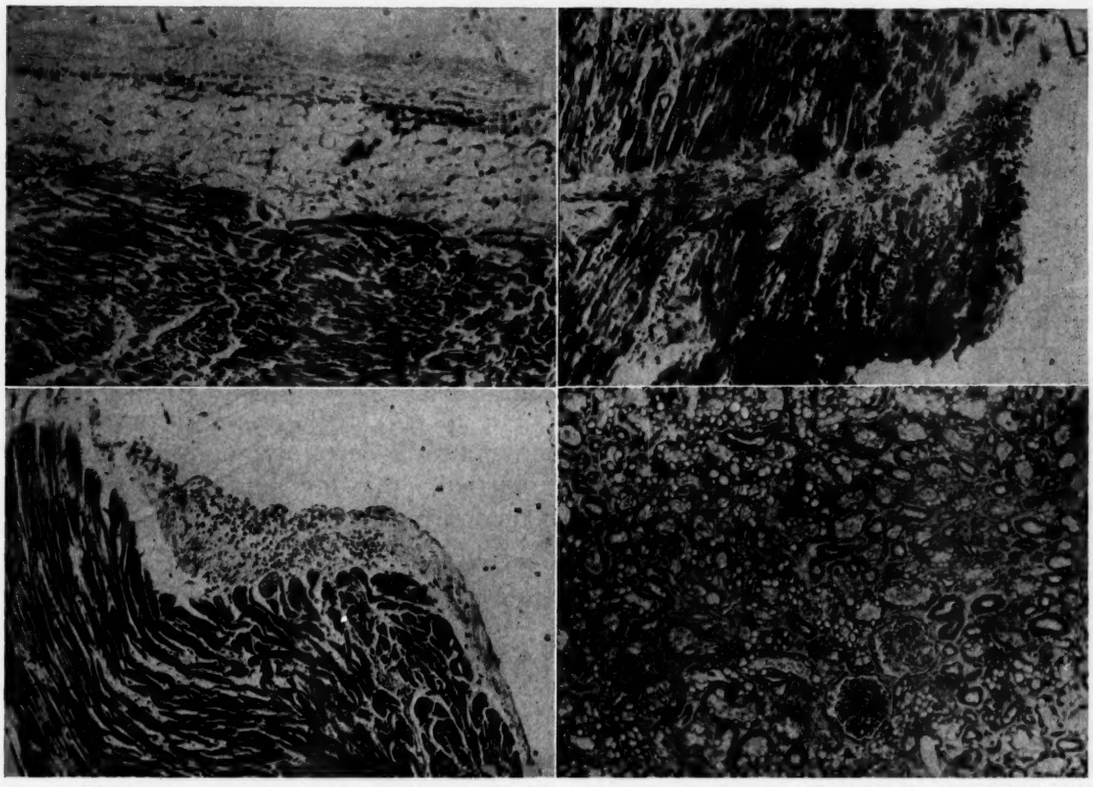

Fig. 3. Photomicrograph showing a mild, non-specific inflammatory reaction in the sub-epicardial tissues manifested by infiltration of lymphocytes and segmented neutrophils. × 150.

Fig. 4. Photomicrograph showing a typical myocardial lesion with necrosis of muscle, infiltration of segmented neutrophils and beginning fibrosis. × 150.

Fig. 5. Photomicrograph of an area of endocardium showing focal infiltration of segmented neutrophils without associated necrosis. × 150.

Fig. 6. Photomicrograph of kidney showing marked hydropic degeneration of the proximal and distal convoluted tubules with complete sparing of the loops of Henle; the reaction varies from slight vacuolization to complete necrosis and sloughing of the epithelium. Aside from a slight proliferation and vacuolization of the epithelial cells of Bowman's capsule, glomerular changes are minimal; hematoxylin and eosin stain. × 150.

lymph node presented only non-specific changes with no evidence of tuberculosis.

The heart, although grossly normal, presented a number of microscopic changes. The epicardium was not thickened; however, there was a mild, non-specific inflammatory reaction in the sub-epicardial fat. (Fig. 3.) The predominant alteration in the myocardium consisted of small areas in which there was loss of muscle striation, varying degrees of necrosis, infiltration of segmented neutrophils and beginning fibrosis. (Fig. 4.) These lesions, while not abundant, were quite distinctive when found. In other areas there was an infiltration of segmented neutrophils between apparently normal muscle fibers, which may represent a primary phase of the more marked change. A minimal, patchy myofibrosis was also noted in the myocardium. Within the endocardium were small collections of lymphocytes and segmented neutrophils indicative of focal endocarditis. (Fig. 5.) This process, although resulting in slight endocardial thickening, showed no necrosis and was not associated with the presence of bacteria or verrucae.

The most unusual and significant histologic changes were encountered in the kidneys where microscopy showed a marked vacuolization of the tubular epithelium. (Fig. 6.) This process most markedly affected the proximal convoluted tubules, the distal convoluted tubules to a lesser degree and completely spared the loops of Henle. The amount of vacuolization varied considerably among tubules for in some the normal epithelium was completely replaced by large colorless vacuoles surrounded by only an outline of cell membrane, while in others only a few small vacuoles appeared within the acidophilic cytoplasm of relatively normal epithelial cells. Not infrequently large vacuoles were en-

countered which were most likely due to the confluence of a number of smaller ones. In still others the vacuoles had apparently ruptured, leaving only a small remnant of cytoplasm adherent to the membrana basalis. Most of the tubules contained faint staining structures within their lumena which had the appearance of fat droplets; however, differential staining revealed that neither these structures nor the vacuolated cells contained fat. Unfortunately, since the tissues had been fixed in formalin, a stain for glycogen was unobtainable. A few hyalinized glomeruli were encountered and occasionally a Bowman's space was seen to contain a granular precipitate. The lower nephrons and collecting tubules were not unusual, revealing only occasional granular casts within their lumina.

COMMENT

This case presents the following interesting aspects: (1) chronic diarrhea of probable functional origin resulting in marked depletion of body potassium; (2) electrocardiographic changes characteristic of potassium deficiency; (3) death during intravenous infusion of glucose which caused a critical fall in the serum potassium and (4) pathologic lesions in the heart and kidneys, most likely produced by potassium deficit.

Muscular weakness, fatigue, hyporeflexia, hypotension and tachycardia are symptoms commonly associated with hypopotassemia. The prolonged inadequate food intake, diarrhea and decreased intestinal absorption, and the daily intravenous therapy were adequate reasons to suspect a deficiency of body potassium in this patient. Therefore, the diagnosis of hypopotassemia was made clinically and emergency therapy with KCl was instituted. The laboratory confirmed our clinical impression.

Two cases of the sprue syndrome, one terminating in lymphosarcoma of the small intestine, which displayed hypopotassemia and deficit of intracellular potassium as demonstrated by the use of potassium balance studies have been described.[16,17] These patients both showed the marked muscular weakness that was noted in our case. Darrow has demonstrated that severe depletion of potassium was responsible for the high mortality of diarrhea in infants[13] and Govan and Darrow[14] have substantially lowered the mortality rate of that disorder by therapy which includes potassium chloride.

Circulatory insufficiency or shock may be responsible for a normal or higher than normal serum potassium level in the presence of marked depletion of intracellular potassium[8,13] and may add to body potassium loss. The chronic dehydration and hypotension manifested by our patient may explain why the initial low serum potassium level of 3.75 mEq./L. was not even lower. The effect of postmortem anoxia on cellular membranes certainly might explain the low normal value for potassium in the blood taken from the heart after death.

Our electrocardiographic tracings are very similar to those in a case of familial periodic paralysis with a serum potassium level of 11 mg. per cent (2.81 mEq./L.).[22] These authors showed return of the S-T segment to the iso-electric line after an oral dose of potassium chloride without any elevation in the serum potassium level. Tarail[19] found low amplitude of T waves and prolongation of the Q-T interval in three of four patients with renal disease associated with low serum potassium. In addition to these changes a very prominent U wave has been observed in a small group of cases with hypopotassemia. The U wave could be abolished by the intravenous administration of potassium chloride.[20] In electrocardiographic investigation of cases of diabetic acidosis it has been found that only T wave depression correlated well with hypopotassemia.[21] Our case shows prolongation of the Q-T interval, sagging of the S-T segment, flattening of the T wave and the appearance of a large U wave, with improvement of some of these abnormalities during the administration of potassium chloride. It is apparent that not enough potassium chloride was given. The elevation of the S-T junctions in AVL and AVR with reciprocal depression in the precordial leads (Fig. 2) indicates injury to the subendocardial myocardium.[28] This was probably due to physiologic injury rather than to the pathologic lesions demonstrated at

necropsy because of the rapid return of the S-T segments toward the iso-electric level during potassium chloride administration.

It is reported that the oral administration of glucose[18] to a patient with familial periodic paralysis may provoke an attack, and it has been shown experimentally that oral glucose given to normal individuals causes a fall in serum potassium. This is thought to be due to the formation of a potassium-hexose-phosphate compound in the cycle of carbohydrate metabolism with consequent intracellular deposition of potassium. We believe that the intravenous administration of glucose to our patient without concomitant use of sufficient potassium was unfortunate and should serve as a lesson in the management of conditions in which potassium deficiency may be present.

A deficiency of potassium ions associated with pathologic lesions in experimental animals was first described in 1937.[25] Although histopathologic changes were noted in the heart, kidneys, pancreas and intestines of the test rats, only those described in the heart and kidneys were constant and have subsequently been confirmed by other investigators. Characteristic lesions in the heart consisted of myocardial and endocardial necrosis with replacement by scar tissue and infiltration by numerous phagocytes. "Diffuse tubular nephritis" was present in all cases observed as evidenced by edema, vacuolization and sloughing of the tubular epithelium. Similar myocardial lesions have been noted in rats and hogs fed diets inadequate in potassium and vitamin B_6.[26] Darrow and Miller[23] were able to produce myocardial lesions in rats either by prolonged injections of desoxycorticosterone acetate or by maintenance on potassium deficient diets. They reported that these changes, consisting only of necrosis and subsequent myofibrosis, were not prevented by an excess of thiamin or pyridoxine or aggravated by suboptimal doses. They believe these lesions are of sufficient severity to cause cardiac failure, and subsequently they have postulated that such changes may be of significance in the production of heart failure in patients with Addison's disease who are overtreated with desoxycorticosterone acetate. Darrow states[8] that myocardial necrosis has been observed in Addisonian patients dying following the administration of desoxycorticosterone acetate, but does not describe these lesions. Follis, Orent-Keiles and McCollum[24] have described histopathologic changes in the myocardium and kidneys of potassium-deficient rats identical with those reported by Schrader et al.;[25] however, they failed to find alterations in any of the other organs. It is their contention that the discrepancies noted by the various investigators can be attributed to the differences in test diets and possible concomitant inanition or vitamin deficiencies.

Despite recent widespread interest in the causes and prevention of potassium deficiency states in man, an exhaustive survey of the literature reveals only one article pertaining to the pathologic alterations associated with this condition. A case has been reported in which a patient with chronic gastroenterocolitis and a minute carcinoma of the pancreas presented clinical and laboratory evidence of hypopotassemia prior to death.[29] At necropsy, in addition to the above entities, renal changes were demonstrated to be entirely analogous to those noted in experimental animals maintained on potassium deficient diets.[24,25] These kidneys presented histopathologic changes characterized by edema, marked vacuolization and sloughing of the proximal and distal convoluted tubular epithelium with minimal glomerular involvement. Further differential staining showed the large vacuoles in the tubular epithelium to contain neither lipoid material nor glycogen. In reporting these findings the descriptive term "clear cell nephrosis" was proposed but these renal lesions were not attributed to the potassium deficit. No changes were demonstrated in the heart. However, as Darrow and Miller[23] have cautioned, cardiac lesions in experimental animals may be difficult to locate; and it is entirely possible that a more thorough search might

have revealed their presence. Although the role of potassium deficiency in the production of renal changes in humans has not been emphasized, there would appear to be adequate substantiation for such a contention in view of the well controlled animal experiments previously cited and because of the findings in our case.

The renal changes in our case were identical to those described as "clear cell nephrosis" and probably represent a marked degree of hydropic degeneration. We were unable to obtain a differential stain for glycogen since the tissues previously had been fixed in formalin. The cardiac lesions were not nearly as prominent as those in the kidney and it was only by studying multiple sections that the described changes were observed. When found, the myocardial lesions presented the typical picture of necrosis, leukocytic infiltration and early fibrosis which has been described in animal experiments. It is most probable that the subepicardial and endocardial changes represent a less marked manifestation of the same process.

We believe that the lesions in the heart and kidneys are due to potassium deficiency and are analogous to those seen in experimental animals. These lesions have not been previously reported in humans as a result of potassium deficit. In order to substantiate this etiologic relationship further study of necropsy material is indicated in established cases of hypopotassemia.

SUMMARY

1. A case of chronic diarrhea is reported which exhibited clinical, laboratory and electrocardiographic evidence of potassium deficiency.

2. Death occurred during intravenous infusion of 10 per cent glucose in the presence of an established potassium deficit.

3. The focal myocardial necrosis, cellular infiltration and fibrosis, focal endocarditis and marked hydropic degeneration of the renal tubules found at necropsy are identical to those lesions reported in potassium deficient animals.

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Severe Hypoplastic Anemia Following Anticonvulsant Medication*

Review of the Literature and Report of a Case

WILLIAM R. BEST, M.D. *and* JEROME T. PAUL, M.D.
Chicago, Illinois

For many years phenobarbital and dilantin sodium have been the principal drugs employed in the treatment of epilepsy. Recently several new anticonvulsant drugs have been introduced. These include tridione (3,5,5-trimethyloxazolidine-2,4-dione),[13] mesantoin (3-methyl-5,5,-phenyl-ethyl-hydantoin),[1] and thyphenytoin (5,5-phenyl-thienyl-hydantoin).[17] Toxic reactions of a serious nature attributable to these drugs have been infrequent. However, several reports of severe hematologic reactions have recently appeared in the literature. In September, 1946, Harrison, Johnson and Ayer[11] reported the first case of fatal aplastic anemia following the use of tridione and mesantoin. Simultaneously Mackay and Gottstein[16] recorded another case of fatal aplastic anemia due to tridione. Greaves[10] noted the development of neutropenia and agranulocytosis during treatment with tridione. Similar cases implicating both tridione and mesantoin have since been recorded by Braithwaite,[3] Carnicelli and Tedeschi,[4] Aird,[1] Gayle, Lynch and Scherer,[8] Bloom, Lynch and Brick,[2] Frank and Holland[7] and Forster.[6] (Table 1.) Ziskind[18] mentioned another case of agranulocytosis with recovery following mesantoin. Lennox[12] mentions several unreported cases of fatal aplastic anemia possibly associated with mesantoin or tridione which have come to his attention. Two cases occurred at Howard Mental Hospital, Rhode Island, one at the Epileptic Colony of Philadelphia, Denmark, and another was briefly mentioned in a British publication. Gibbs[9] has observed two severe, generalized toxic mesantoin reactions with neutropenia of approximately 2,500. No doubt there have been other unreported cases.

Recently we have observed a case of severe hypoplastic anemia with recovery which occurred after prolonged medication with mesantoin and thyphenatoin as well as phenobarbital and dilantin. This case serves to re-emphasize the potential dangers of these otherwise valuable therapeutic agents.

CASE REPORT

D. C., a white male aged thirty, was first seen in the neurology dispensary in June, 1947, complaining of grand mal seizures with occasional psychomotor components since the age of fourteen. There was no familial history of epilepsy though one sister had suffered from migraine headaches. At the age of ten the patient had fallen from a fourth floor window into soft ground remaining unconscious for approximately twenty minutes but suffering no other apparent ill effects. Otherwise his past history was non-contributory. The character of his attacks had been essentially the same since their onset fifteen years before. He would suddenly fall, lose consciousness and have convulsive movements followed by a period of sleep and sometimes prolonged fugue states with amnesia. Occasionally he would bite his tongue or be incontinent of urine. Attacks occurred at weekly intervals during the first few years. Three and five years after onset there were

* From the Department of Internal Medicine, University of Illinois, College of Medicine, Chicago, Ill. Aided by a grant from the Hematology Research Foundation, Chicago, Illinois.

TABLE I

PERIPHERAL BLOOD FINDINGS OF PATIENTS SHORTLY BEFORE, DURING AND AFTER HOSPITALIZATION

No.	Case Reports	Age	Sex	Medication			Duration of Hypoplastic Symptoms	Initial Blood Study							Outcome
				Drug	Daily Dose (Gm.)	Duration of Therapy		Hgb. (Gm.)	R.B.C $\times 10^6$	W.B.C. $\times 10^3$	Platelets	Reticulocytes %	Polymorphonuclears %	Bone Marrow	
1	Harrison et al[11]	16	F	Tridione	0.3	6 mo.	3–4 mo.	7.6	3.1	1.0	42,000	0.1	5	Hypoplastic	Death
				Mesantoin	0.3	5 mo.									
2	Mackay and Gottstein[16]	23	F	Tridione	1.8	10 mo.	5 days	4.8	1.55	4.25	17,000	0.5	15	Normal	Death
3	Greaves[10]	25	F	Tridione	1.8	2½ wk.	2 wk.	12.8	4.26	1.9	.....	...	52	.....	Recovery
4	Braithwaite[3]	11	M	Tridione	1.2	7½ wk.	12 days	....	2.73	0.8	Adequate	...	0	Hypoplastic	Death
5	Carnicelli and Tedeschi[4]	19	F	Tridione	0.9	5 mo.	16 days	10.5	2.33	1.6	5,000	0.0	4	Hypoplastic "blasts"	Death
				Dilantin	0.3	3 mo.									
6	Aird[1]	26	F	Mesantoin	0.3–0.4	7½ mo.	1 wk.	....	1.14	2.5	.....	...	2	.....	Death
7	Gayle et al.[8]	11	F	Tridione	1.0	5½ mo.	1–2 mo.	8.3	2.3	2.5	40,000	...	6	Hypoplastic	Death
				Diphenylene	?	13 mo.									
8	Bloom et al.[2]	34	F	Mesantoin	0.2	9 mo.	1 mo.	6.1	2.06	0.7	70,000	0.0	24	Hypoplastic	Recovery
9	Frank and Holland #1[17]	16	M	Mesantoin	0.3–0.4	7½ mo.	4 mo. worse—7 wk.	10.5	3.38	1.4	70,000	...	34	Hypoplastic	Death
10	Frank and Holland #2[27]	31	M	Mesantoin	0.3	5½ mo.	1 mo.	4.8	2.1	0.3	10,000	0.5	0	Hypoplastic	Recovery
11	Forster[6]	36	M	Mesantoin	0.15–0.4	8 mo. discontinued 2 mo. prior)	5 mo. worse—1 mo.	....	1.2	1.6	.....	...	61	Hypoplastic	Death complicated by heart failure
				Phenurone	1.5	2 mo.									
12*	Gentry and Hill[19]	6½	M	Tridione	?	3 wk.	2 days	9.6	2.79	2.7	Adequate	...	2	Hypoplastic	Death
13	Briggs and Emery[20] (Case #9)	9	M	Tridione	?	11 mo.	Detected on routine blood counts	....	3.3	2.5	Less than 500	...	10	Hypoplastic	Recovery
14	England and McEachern[21]	24	F	Mesantoin	0.3	10 mo.	6 days	7.6	2.3	1.5	60,000	Less than 1.0	7	Hypoplastic	Death
15	Forster, Watson and Neumark[22]	11	M	Tridione	0.9–1.2	6 mo.	Detected on routine blood counts	13.4†	4.3	2.6	40,000	...	2	Hypoplastic	Death
16	Weller and Metcalfe[23]	31	M	Mesantoin	0.1	6 mo.	2 days	9.8	3.35	1.85	36,000	...	14	Hypoplastic	Death
17	Present Case D.C.	30	M	Dilantin	0.3	8 yr.	1½ mo.	3.0	0.92	3.0	Marked reduction	0.5	26	Hypoplastic	Recovery
				Mesantoin	0.3	13 mo.									
				Thyphenytoin	0.26	5 mo.									

* Cases 12–16 were noted after paper submitted for publication.

† Figures given four weeks after medication stopped, a few days prior to death. This case was followed throughout medication. Granulocytopenia responded to discontinuation of medication and recurred fatally after therapy resumed.

episodes of status epilepticus. He had frequent psychomotor attacks during this period. Bromides were prescribed during the first few years. He had been given varying doses of phenobarbital for eleven years and dilantin for eight years.

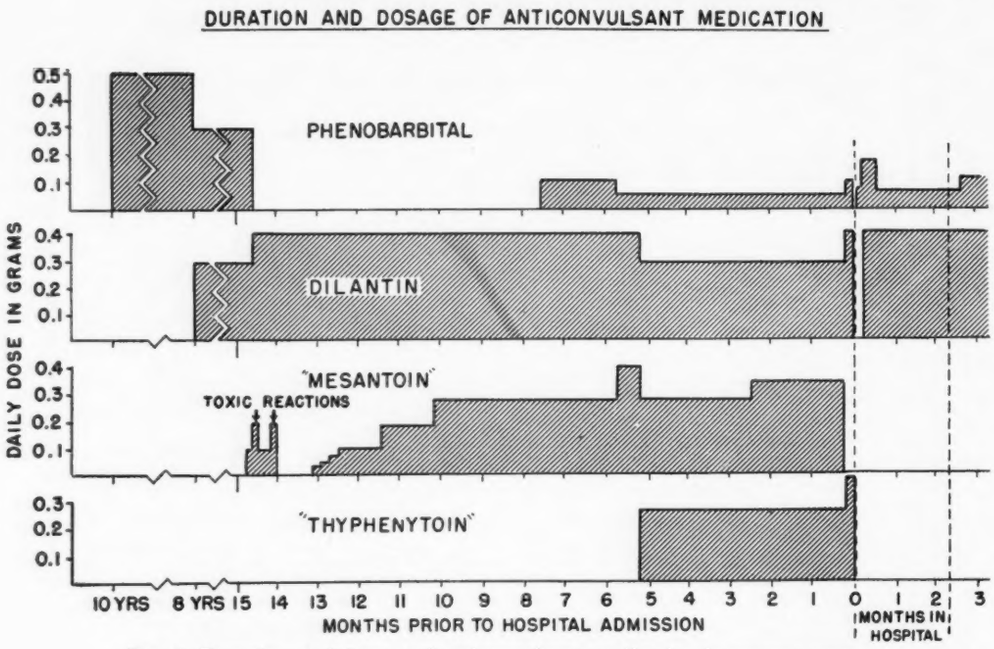

FIG. 1. Duration and dosage of anticonvulsant medication in present case.

An electroencephalogram in July, 1947, shortly after admission to the clinic was reported by Dr. F. A. Gibbs as follows: "Psychomotor focus in left anterior temporal area. Also generalized spikes. Background activity moderately abnormally fast." Due to failure of former medication adequately to control his convulsive seizures and psychomotor states mesantoin (0.2 Gm. daily) was prescribed. Within a week he manifested a toxic reaction characterized by lymphadenopathy, skin rash, fever and sore throat. Mesantoin dosage was reduced briefly then reinstated with exacerbation of the toxic manifestations. It was stopped completely for about one month following which it was prescribed in small but gradually increasing doses without further toxic reactions. (Fig. 1.) In May, 1948, thyphenytoin (0.26 Gm. daily) was added without toxic reaction. During the subsequent period seizures occurred approximately once a month and psychomotor attacks were well controlled.

In July, 1948, he began to notice spotting of blood on his pillow frequently upon awakening. On August 25, 1948, he presented himself to the clinic with malaise, sore throat and weakness of one week's duration. Examination revealed cervical adenopathy and fever of 102.4°F. Mesantoin was discontinued. Laboratory work-up revealed an erythrocyte count of 1,400,000 and a leukocyte count of 4,550 with 61 per cent neutrophils and 39 per cent lymphocytes. August 31st he returned with increased severity of these symptoms showing marked weakness and pallor and having a temperature of 103°F. He was admitted as an emergency patient to the medical service of the Illinois Research and Educational Hospitals.

Physical examination on admission revealed marked pallor and weakness, slight cervical adenopathy, an apical systolic murmur and many recent and older bilateral flame-shaped retinal hemorrhages. He appeared acutely ill. Temperature was 101.6°F., pulse 100, respirations 28, blood pressure 100 systolic and 50 diastolic.

Laboratory examination showed an erythrocyte count of 920,000, hematocrit 8 per cent, corrected sedimentation rate (Wintrobe) 2 mm., leukocytes 3,000, neutrophils 26 per cent and lymphocytes 74 per cent. Platelets were markedly reduced on smear. Sternal marrow study (Limarzi concentration technic)[14] revealed 1 per cent nucleated cell layer with marked depression of all normal elements, especially megakaryocytes. There was a moderate relative lymphocytosis of the bone marrow. (Fig. 2.) Reticulocyte count a few days after admission was 0.5 per cent

Urinalysis and blood chemistries (NPN, glucose and chlorides) were within normal limits.

All medication was stopped and the patient was given seven half-liter, whole-blood transfusions during the first eight days of hospitalization bringing the erythrocyte count up to 3,720,000. No further transfusions were necessary. Crude liver extract (1.0 cc. intramuscularly daily) was administered from the fourth through the fiftieth hospital days. On the third hospital day he experienced a grand mal seizure following which phenobarbital and dilantin were prescribed. Six days after admission petechiae were noted on the legs. Vitamins C (500 mg. daily at first, then 200 mg. daily) and K (hykinone 2.4 mg. intramuscularly daily) as well as thiamine were administered throughout the remainder of the hospital stay.

The temperature gradually receded from a daily mean of approximately 100.6°F. on admission to normal over a period of eighteen days. An acute periapical abscess of a lower left molar was noted on the fourteenth hospital day. The dental consultant called attention to severe general acute periodontosis and periodontitis and recommended full mouth extraction. Consequently all teeth were cautiously extracted over a period of two weeks. The patient was given 300,000 units of procaine-penicillin daily during the period of extraction.

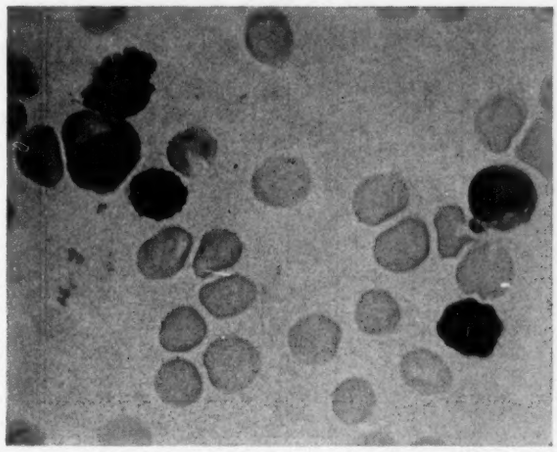

FIG. 2. Photomicrograph of patient's marrow at time of admission (August 31st); note relative lymphocytosis of bone marrow with depression of normal hemopoietic elements. × 1,000.

Reticulocytes remained at approximately 0.5 per cent for the first twenty-five days of hospitalization then gradually rose to 6.2 per cent on the forty-fourth day and stayed at about that level through the remainder of the hospital stay and fell to 2.0 per cent three weeks after discharge. Erythrocyte counts gradually fell from the post-transfusion level of 3,720,000 to 2,510,000 two weeks later. Thereafter they gradually rose to 3,130,000 at time of discharge and 3,620,000 three weeks later. Leukocytes

TABLE II

STERNAL MARROW FINDINGS OF PATIENT DURING HOSPITALIZATION

Date	Hemoglobin (Gm.)	R.B.C. (Millions)	W.B.C. (Thousands)	Hematocrit (%)	Reticulocytes (%)	Platelets	Differential (%)		
							Polymorphonuclears	Lymphocytes	Monocytes
August 25.....	....	1.40	4.55	..	...	.....	61	39	0
August 31 Admission....	3.0	0.92	3.00	8	...	Reduced on smear	26	74	0
	5 Blood Transfusions								
September 6....	10.5	3.25	2.15	31	0.5	Reduced on smear	14	76	10
	2 Blood Transfusions								
September 8....	....	3.72	....	36	0.5				
September 19...	10.0	3.10	3.20	30	0.5				
September 29...	....	2.60	4.00	27	1.3				
October 11.....	6.5	2.68	3.60	28	6.9	Reduced on smear	38	43	9
October 22.....	8.5	2.70	3.70	..	4.6	93,000	59	31	6
November 2....	10.0	3.22	3.25	..	6.9	193,000			
November 8 Discharge.....	11.2	3.13	5.30	38	5.8	89,000	50	50	0
November 29....	13.6	3.62	3.35	42	2.0	80,000	48	40	11

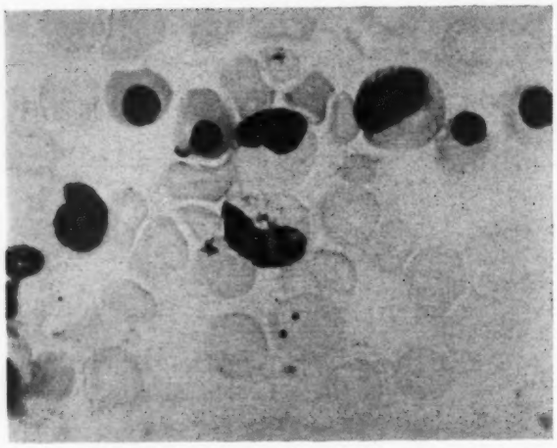

FIG. 3. Photomicrograph of patient's marrow forty-four days after admission (October 11th); note increasing cellularity of hemopoietic elements. × 1,000.

dropped from admission level of 3,000 to 2,150 on the sixth day, then rose with some fluctuations to approximately 3,500 four weeks later. Counts remained near this level with 5,300 on discharge and 3,350 three weeks later. Adequacy of platelets was estimated from smears and occasional platelet counts (modified Dameshek method). They remained reduced throughout the period of observation. Differential counts showed a low of 14 per cent neutrophils on the sixth day increasing gradually to 50 per cent at time of discharge. The hematologic findings are summarized in Table II. Sternal punctures were done at three week intervals. Twenty-two days after admission the picture was essentially the same as on admission with general hypoplasia and relative lymphocytosis of the marrow. On the forty-fourth hospital day the marrow showed increased cellularity with definite normoblastic hyperplasia. (Fig. 3.) Sixty-four days after admission the normoblastic response continued. Table III presents representative differential marrow counts.

TABLE III

SUMMARY OF PERTINENT EINDINGS IN REPORTED CASES OF PANCYTOPENIA FOLLOWING ANTICONVULSANT MEDICATION

	August 31		October 13	
Quantitative Values (per cent)				
Fat (yellow and red)	1.0		1.0	
Plasma	91.0		71.5	
Myeloid-erythroid cells*	1.0		2.5	
Erythrocytes	7.0		25.0	
Qualitative Values (per cent)				
	Per Cent of All Cells	Per Cent of Series	Per Cent of All Cells	Per Cent of Series
Myeloid Series	43.0	..	36.0	
Myeloblasts	....	2	....	3
Promyelocytes†	....	19	....	18
Neutrophilic myelocytes	....	25	....	29
Neutrophilic metamyelocytes	....	30	....	30
Polymorphonuclear neutrophils	....	20	....	16
Eosinophils	....	4	....	4
Lymphocytes	44.5	..	12.5	
Erythroid Series	12.5	..	51.5	
Pronormoblasts	....	0	....	0
Basophilic normoblasts	....	5	....	11
Polychromatic normoblasts	....	38	....	57
Orthochromic normoblasts	....	57	....	32
Myeloid: Erythroid ratio	3.44:1		0.7:1	
Megakaryocytes	None seen on smear		Marked reduction	

* Normal myeloid-erythroid value, 6.8 per cent.
† Includes leukoblasts.

The patient became ambulatory eight days after hospitalization and seizures remained fairly well controlled under dilantin (0.4 Gm. daily) and phenobarbital (60 mg. daily). He was discharged November 10, 1948, in good subjective health after seventy-two days of hospitalization.

At routine check-up in the hematology dispensary twenty days after discharge the patient was feeling fine subjectively and had experienced only one seizure.

COMMENT

The question of which drug or drugs are implicated in this toxic reaction cannot be definitely answered. However, mesantoin is the most likely one in light of reported aplastic reactions following use of this drug alone[1,2,7] as well as in combination with tridione.[11] The general incidence of toxic reactions is higher following mesantoin than following the other anticonvulsants[9] used in this patient. Thyphenatoin, the newest of these drugs, has been used in seventy-three cases over a period of two years by Peterman[17] and in over forty cases at the Illinois Neuropsychiatric Institute[9] without any notable alteration in blood findings. Toxic reactions of all types are infrequent. Figure 4 illustrates the minor structural variations differentiating the hydantoin drugs mentioned in this case report.

It is of value at this time to peruse the assembled data of the several case reports. (Table I.) Several general statements appear warranted: (1) Pancytopenia was secondary to bone marrow aplasia in all

but one case[16] in which marrow was examined. (2) Mesantoin and/or tridione were probably responsible for the pancytopenia in most of the cases. (3) Severe hypoplasia developed after varying periods of therapy ranging from one-half to thirteen months. In most cases treatment had extended for more than five months. (4) Minor symptoms heralding marrow aplasia were often disregarded by the patient. These symptoms were present from five days to four months before hospital admission. In most cases they were present for more than two weeks. (5) None of the usual hematologic studies on admission were related to the ultimate outcome.

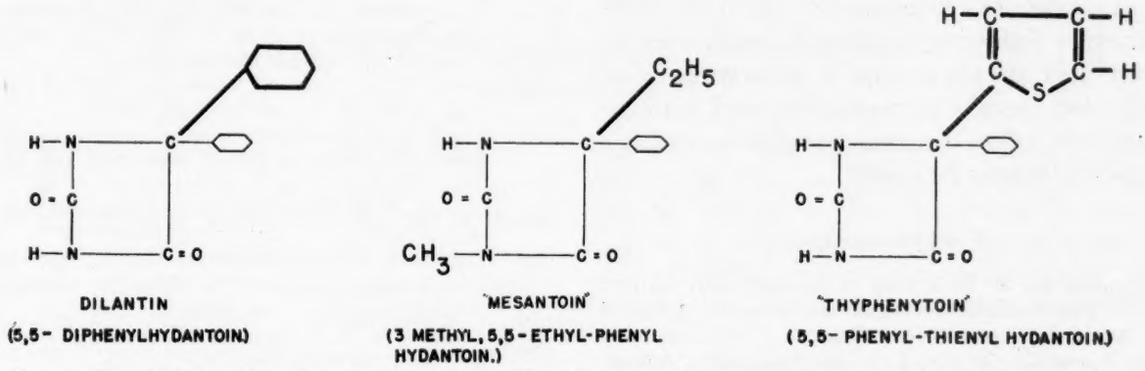

FIG. 4. Chemical formulas of the hydantoin drugs used in therapy of present case emphasizing the prosthetic groups which differentiate them.

In considering prophylactic measures against pancytopenia in the therapy of epileptics various suggestions have been made. Mackay and Gottstein[16] recommend hematologic examination at monthly intervals or sooner for patients receiving tridione. Lennox[5,13] advocates similar intervals of examination. He believes that therapy should be terminated if the leukocytes drop below 4,000 together with a drop in the neutrophilic granulocytes below 40 per cent. Bloom et al.[2] favor monthly blood examinations also for patients receiving mesantoin, recommending cessation of therapy if any element drops rapidly. Lennox[12] has managed approximately 400 cases with tridione or mesantoin without difficulty since instituting monthly blood tests. Gibbs[9] has managed over 100 cases with this routine. He has had no major toxic reactions. Loscalzo[15] advocates weekly blood examinations for the first sixteen weeks during mesantoin therapy. In general he minimizes the importance of routine hematologic investigation. It is to be noted that most of the reported reactions occurred after the first sixteen weeks. Unfortunately, serial blood studies prior to the development of severe hypoplasia of the bone marrow were not obtained in most of the reported cases. According to Davis and Lennox[5] gradual changes were observed in some patients receiving tridione. With careful adjustment of dosage no serious toxic effects resulted. Gradual reduction of red and white counts were observed in Forster's case.[6] Mesantoin was stopped and phenurone* given in its place, nevertheless hypoplastic anemia developed in two months.

From the present study it would seem that not only should the blood be examined periodically but also that the patient should be forewarned of possible toxic symptoms. Suspicious symptoms occurring early in the reported cases include increased tendency to bruise or bleed (oozing gums, epistaxis, metorrhagia) and/or general non-specific symptoms of a type commonly belittled by the laity (weakness, lethargy, malaise, general aches, anorexia and skin rash). Such symptoms in a patient receiving mesantoin or tridione warrant immediate hematologic investigation with cessation of therapy if red cells, white cells or platelets are significantly

* Phenurone is an experimental drug, a phenyl-acetyl-urea compound.

reduced over pre-therapy values. Several cases, including the one herein reported, developed transient, toxic rashes long before the hypoplastic episode became manifest.

SUMMARY

A case of hypoplastic anemia with recovery following medication with mesantoin and thyphenytoin is presented. The reported cases of pancytopenia and agranulocytosis following anticonvulsant medication are briefly reviewed.

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Pheochromocytoma with Neurofibromatosis*

FRANK W. DAVIS, JR., M.D.,
Biltmore, North Carolina

JOHN G. HULL, M.D. *and* JAMES C. VARDELL, JR., M.D.
Baltimore, Maryland

THE syndrome caused by tumors of chromaffin origin which produce a pressor substance has been more or less clearly defined during the past several decades.[1–4] These pheochromocytomas may arise wherever chromaffin tissue exists, most commonly in the adrenal medulla but occasionally in Zuckerkandl's organ or in the thoracic or abdominal sympathetic ganglia. They are usually benign, sometimes malignant, generally unilateral, though occasionally bilateral or multiple,[1,2,5] varying in weight from 10 to 2,000 Gm. They may give rise either to paroxysmal or sustained hypertension which, in combination with other epinephrine-like effects (headache, anxiety, pallor, sweating, palpitation, etc.), constitutes the cardinal feature of the clinical picture.

Prior to the present decade suspicion of the presence of a pheochromocytoma was aroused only by attacks of paroxysmal hypertension, which sometimes could be reproduced by pressure over the adrenal region. Demonstration of an adrenal tumor by palpation, pyelography and sometimes by perirenal air insufflation was frequently possible. In a few cases[6] a pressor substance could be demonstrated in the blood stream during a paroxysm. Since 1945 several apparently reliable confirmatory tests have been described as aids in reaching a definitive preoperative diagnosis. The advantages of two of these tests are evident in the following case.

CASE REPORT

E. S., a thirty-eight year old white laborer, was admitted to The Johns Hopkins Hospital on July 23, 1948, complaining of nausea, excessive perspiration and weakness, which had been present for six weeks. There was no family history of hypertension, heart disease, diabetes or neurofibromatosis. For many years the patient had noticed the presence of multiple soft painless nodules and of several areas of brown pigmentation over his entire body surface.

Five years prior to admission the patient was awakened by severe pain behind the left sternocleidomastoid muscle and he noted marked swelling in this area. Concomitant with his awareness of the swelling he realized that his vision was blurred. Examination disclosed a systolic blood pressure of 280 mm. of Hg and glycosuria. He was hospitalized and the swelling was treated with ice packs, following which the swelling and tenderness gradually subsided in the course of several months. The glycosuria was no longer present at the end of six months and he was allowed to discontinue a restricted carbohydrate diet. During the six months following the acute episode his visual symptoms gradually cleared, he was told that his blood pressure had returned to normal and he was able to resume his usual activity.

Following recovery from this illness the patient remained entirely asymptomatic until six weeks before his admission to The Johns Hopkins Hospital. Again without previous incident he awoke one morning with nausea, vomiting, weakness and blurring of vision. During the ensuing six weeks these symptoms persisted and he developed episodes of profuse perspiration apparently unrelated to activity, eating or position. Anorexia led to the loss of 15 pounds in weight. On two occasions his blood pressure was recorded at 250/150 and 170/120 mm. of Hg. He was thought to be suffering from malignant hypertension and was referred for hospitalization and possible sympathectomy.

* From The Medical Clinic, The Johns Hopkins Hospital, Baltimore, Md.

Physical examination on admission to The Johns Hopkins Hospital revealed tachycardia of 100 with an initial blood pressure of 150/110. The patient was well developed but showed evidence of moderate recent weight loss. His skin was cold, clammy and profuse perspiration was apparent. There were multiple intra- and subcutaneous soft nodules which ranged in size from 2 to 15 mm. in diameter; these were slightly moveable and non-tender. There were multiple café-au-lait spots. Examination of the eye grounds revealed pallor of the optic discs with marked narrowing of the retinal arterioles and moderate arteriovenous compression. There were a few white perivascular lines and scattered white shiny exudates. The retinal veins showed considerable tortuosity, with several varices in the macular and perimacular areas. There were one or two small hemorrhages in the peripheral regions of the fundi and degenerative and pigmented changes were present about the maculae. There were bilateral central scotomas.

The thyroid gland was not enlarged; the lungs were clear; the heart was within normal limits in size, the left border extending to the mid-clavicular line in the fifth interspace. At the apex there was a loud, low-pitched systolic murmur, with a high-pitched shrill component varying somewhat in intensity. Likewise a systolic murmur was audible in the pulmonic area and the aortic second sound was accentuated. Peripheral pulsations were full and equal. Abdominal examination disclosed no abnormal findings. The remainder of the physical examination was not remarkable.

The hemoglobin, red blood count, hematocrit, white blood count and differential were entirely normal. The serologic tests for syphilis were negative. Urine examination was normal. Preoperative phenolsulfonephthalein excretion over a two-hour period was 37 per cent. The nonprotein nitrogen, calcium, phosphorus and urea nitrogen concentrations in the serum were normal. The fasting blood sugar, however, was 136 mg. per 100 cc. of blood and an oral glucose tolerance test (1.25 Gm./Kg.) preoperatively revealed a diabetic curve. (Fig. 1.) Determination of 17-ketosteroids in the urine was 12.2 mg./24 hours. The basal metabolic rate was +54 per cent, cholesterol 335 mg./100 cc. of serum.

Teleoroentgenogram and fluoroscopy of the chest were normal. Intravenous pyelogram showed kidneys that were normal in size, shape and position, without evidence of suprarenal masses. Radiographic examination of the spine revealed no abnormalities. An electrocardiogram demonstrated sinus tachycardia, with unusually high P waves; there were changes in the unipolar limb leads which were thought to be consistent with clockwise rotation of the heart on its long axis and displacement of the apex somewhat to the right.

Preoperatively the hospital course was concerned largely with diagnostic procedures in reference to blood pressure changes as influenced by the conditions and drugs charted in Figure 1. The random daily blood pressures varied from 150–185 systolic, 110–135 diastolic. Sedation and cold pressor results are also shown in Figure 1. The intravenous histamine test (0.025 mg. of histamine base) produced the striking result illustrated, with a brief drop in blood pressure from 160/115 to 115/60, followed within sixty seconds by a precipitous rise to 290/180, falling gradually over a two-hour period to the original level. During this test the patient experienced a severe generalized headache and demonstrated profuse perspiration and widely dilated pupils. On a later day administration of 20 mg. of piperidylmethyl benzodioxane (933 F) intravenously[7] produced a fall in blood pressure from a control level of 170/120 to a minimum of 92/60 at three minutes, with a gradual rise to the previous level after ten minutes. During the hypotensive period the patient became flushed, tachypneic and developed cardiac irregularities (first bigeminal rhythm, followed by trigeminy and later multiple, irregularly spaced premature contractions).

Attempts to reproduce an attack of paroxysmal hypertension by means of massage of the adrenal regions and carotid sinuses, and by alteration of body position were unsuccessful.

The history, physical findings and results of the above described procedures were thought to be diagnostic of a pheochromocytoma although the location of the tumor was not apparent. It was deemed wisest to carry out a careful abdominal exploration by the anterior approach and on August 4, 1948, under sodium pentothal followed by gas, oxygen and ether anesthesia, Drs. W. W. Scott and J. A. C. Colston performed a transverse upper abdominal incision, extending from flank to flank. The right adrenal was explored and found to be normal. On exploration of the left adrenal area a firm, rounded, encapsulated tumor was found posterior to the adrenal gland. The tumor, with a portion of the left adrenal, was rapidly excised

following ligation of the vessels supplying the tumor. Immediately after ligation of the vessels the blood pressure fell, becoming unobtainable, and the carotid pulse was not felt. At this point 1.5 gm. of epinephrine was injected into the tubing of a previously flowing intravenous infusion, and a continuous infusion of a solution containing 1 mg. of epinephrine/100 cc. of normal saline was instituted. The blood pressure immediately responded with a rise to 135/110 and was maintained at approximately this level by the continued infusion of epinephrine, while the remaining chromaffin-bearing areas were explored and a biopsy of an intracutaneous nodule was performed. In addition to the epinephrine in saline, 400 cc. of whole citrated blood was administered.

It was necessary during the first twenty-six postoperative hours to introduce the epinephrine infusion continuously. During this period a total of 50.4 mg. of epinephrine was administered in vehicles of normal saline or 5 per cent glucose to which had been added potassium chloride (total KCl-2.0 Gm. for twenty-four hours). Serum potassium level at this time was 3.7 mEq./L. The blood pressure fluctuated widely during this period, ranging from 60–200 systolic and 0–120 diastolic, and even minimal alterations in rate of flow of the epinephrine infusion produced striking changes. Constant supervision of the patient by the house physicians was necessary in order to regulate the epinephrine intake which gradually but irregularly was decreased until at the end of twenty-six hours the blood pressure stabilized spontaneously at approximately 110–120/60–80. During the first three postoperative days intestinal decompression was accomplished by a preoperatively introduced Miller-Abbott tube. By the fourth day intravenous alimentation was no longer necessary.

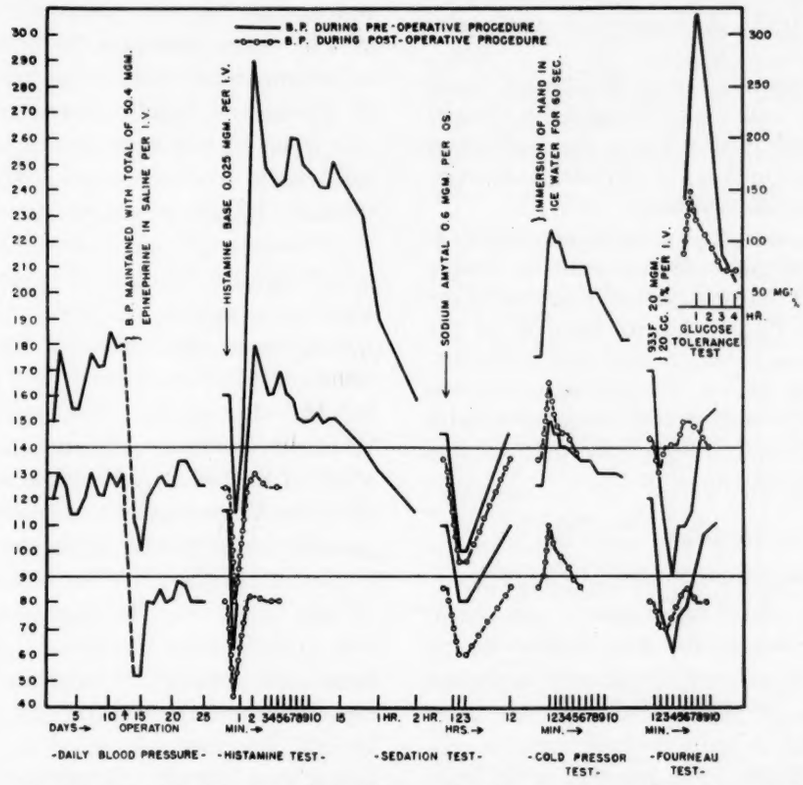

FIG. 1. Composite diagram of the effect on the blood pressure of the drugs and procedures utilized in the diagnosis and management of this patient with pheochromocytoma. The pre- and postoperative pressures are superimposed.

During convalescence repetition of the preoperatively abnormal tests yielded normal values as shown in Figure 1. The histamine and benzodioxane tests became entirely normal, the glucose tolerance test resulted in a non-diabetic curve, the basal metabolic rate fell to +17 per cent, and phenolsulfonephthalein excretion increased to 51 per cent.

Examination of the tumor showed a 4.5 by 3.5 by 3 cm. mass weighing 25 Gm. which was

symmetrical, red, partially encompassed by areas of thinned out adrenal cortex. Microscopic examination of sections fixed in chromate solution, and with periodic acid stains, showed sheets of tumor cells containing large quantities of brownish cytoplasm. The nuclei were large, uniform and vesicular. The cells for the most part were uniform with a tendency to form alveolar clusters.

Microscopic examination of the dermal lesion demonstrated a well defined nodule composed of small spindle-shaped and angular nuclei and cells, with large numbers of parallel and interlacing connective tissue fibers.

The postoperative course following stabilization of the blood pressure was entirely benign and it was noted that the cardiac murmurs were far less striking than prior to removal of the tumor. The blood pressure averaged 130–140/85–95 during the period of observation and the patient was discharged greatly improved, with a diagnosis of pheochromocytoma (left adrenal gland) and neurofibromatosis.

COMMENT

The occasional association of neurofibromatosis with chromaffinomas has been pointed out recently by MacKeith[1] in his review of the 165 cases of pheochromocytoma reported prior to 1944. Of these 165 cases nine were found to have concomitant neurofibromatosis. Since 1944 reports of at least thirty-seven cases of pheochromocytoma have been published in none of which was this association noted. The explanation of the incidence of neurofibromatosis in persons with pheochromocytoma is not immediately forthcoming but it seems worthy of note that in 10 of the 203 cases now in the literature the two disorders were co-existent.

The angiospastic retinitis in this case represented an exacerbation or repetition of a similar attack five years previously from which slight secondary optic atrophy persisted. Bruce[8] points out that even in cases in which the vasospasm is entirely relieved, retinal changes persist for many months or longer. Similarly, the renal function, though tending to improve, remained impaired following operation.

The production of a typical hypertensive paroxysm in a patient with a pheochromocytoma by the use of intravenous histamine was first achieved in 1943 by Hyman and Mencher[6] but it remained for Roth and Kvale[9] to suggest its use as a test for the presence of this tumor. In the Mayo Clinic cases a significant increase in blood pressure (exceeding the cold pressor rise by 100 mm. of Hg) was consistently produced by the injection intravenously of 0.025 to 0.05 mg. of histamine base. The striking effect of this drug in our case is charted in Figure 1 on which it can be seen that the rise in systolic blood pressure from 160 to 290 within sixty seconds was strongly suggestive of a sudden release of epinephrine or a similar pressor substance.

Further confirmation of the clinical diagnosis of pheochromocytoma was obtained by the use of the Fourneau drug 933 F (piperidylmethyl benzodioxane), as described in 1947 by Goldenberg et al.[7] as a diagnostic procedure in the presence of pheochromocytoma with the adrenal-sympathetic syndrome. The adrenolytic effect of this and other benzodioxane derivatives led to their trial in cases of pheochromocytoma, and in each of the four cases reported by Goldenberg significant reduction in blood pressure was noted in contrast to the usual rise found in normal controls and other varieties of hypertension. The usefulness of these drugs has been further affirmed by Ganem and Cahill.[10]

The hypermetabolism in this case is consistent with previous reports in which elevated basal metabolic rates were noted[10,11] but other evidences of thyrotoxicosis were absent. The BMR fell to +17 per cent following removal of the tumor.

Abnormalities of carbohydrate metabolism may or may not be demonstrable in the presence of pheochromocytoma.[1,2,12] Glycosuria and hyperglycemia are not uncommonly found during the paroxysms of hypertension. In this case the history of glycosuria during the first symptomatic hypertensive episode five years prior to admission to the hospital led to suspicion of a chromaffin tumor. The presence of a diabetic type of glucose tolerance test after

hospitalization was confirmatory and there was a striking change to a normal curve postoperatively. A dramatic demonstration of the effect of an adrenal medullary tumor on carbohydrate metabolism was that presented by the case reported by Duncan et al.[12] in which classical diabetes mellitus was the presenting disorder yet the removal of a pheochromocytoma permitted carbohydrate metabolism to become normal, with a normal glucose tolerance test.

The interval of five years during which our patient remained asymptomatic following the initial episode of hypertension is unusual in the presence of this tumor, but a symptom-free interval of ten years has been reported[13] and others of as long as six years.[2] Since 10 per cent of these tumors are bilateral[1] and 15 per cent are extra-adrenal[7] or multiple,[5] and since only by the abdominal approach can all of the subdiaphragmatic chromaffin-containing areas be examined, an anterior abdominal incision was believed the operation of choice.

The difficulty in maintaining a stable blood pressure during the immediate postoperative period is a formidable one and rapid fluctuations characterize this phase. Minimal alteration in the rate of flow of the epinephrine infusion effected as great a change in systolic pressure as 150 mm. of Hg. The use of continuous intravenous epinephrine infusions has been suggested by other observers,[1,3] and previous experience in The Johns Hopkins Hospital supports the fact that this technic is of great usefulness.[14]

Small amounts of supplementary potassium were used in this case during the phase of epinephrine infusion because of the well known effect of epinephrine and glucose on the serum potassium level.[15,16]

SUMMARY

1. A case of pheochromocytoma associated with neurofibromatosis, the tenth such association noted in the literature, is reported.

2. The usefulness of several recently described diagnostic procedures is emphasized.

3. The effect on metabolism and carbohydrate tolerance seen occasionally with this tumor is again demonstrated.

4. Several aspects of the management of patients following the removal of pheochromocytomas are briefly discussed.

We were fortunate in securing the advice and assistance in the management of this case of Drs. J. E. Howard, George Dana, Evan Calkins and Joseph King who have been studying extensively the problem of pheochromocytoma.

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Book Reviews

The Ciba Collection of Medical Illustrations. A Compilation of Pathological and Anatomical Paintings. Prepared by Frank H. Netter, M.D., 224 pages, 191 full-color plates. Summit, N. J., 1948. The Ciba Pharmaceutical Products, Inc. *Price* $6.50.

Dr. Netter, well known medical illustrator, has incorporated in this volume a number of his justly popular water-color illustrations of pathologic and anatomic subjects of general medical interest. The compilation includes a series of illustrations, with detailed explanatory legends, of lungs and chest, injuries to the chest; esophagus, stomach, duodenum, small intestine, large intestine, injuries of the abdomen; the testicle, prostate, male breast, female breast; the heart and aorta—in all, 191 full-color plates. Printed on heavy-weight gloss enamel stock, elegantly designed and handsomely bound, the portfolio provides esthetic as well as didactic satisfaction.

The Ciba Pharmaceutical Products, Inc., for whom these illustrations originally were made over an eight-year period, has made this volume available (on direct request to the company only) at cost and, in view of soaring publication costs, at a gratifying price. This is a fine example of what the pharmaceutical houses, with their wide resources and alert initiative, can do in the field of medical education.

A.B.G.

On Hospitals. By S. S. Goldwater, M.D., 392 pages. New York, 1947. The Macmillan Company. *Price* $9.00.

"On Hospitals" is a collection of individual writings of Dr. S. S. Goldwater, covering a period of forty years of hospital administration, edited by his wife, Clara A. Goldwater. Mrs. Goldwater, assisted by highly competent advisors, has arranged the book into five sections as follows: On Administration and Organization; Hospital and Doctor; Hospital, Patient and Community; Planning, and Hospital Plans. The book also contains a selected bibliography of the writings of Dr. Goldwater. The book is of convenient size, printed on good quality paper and the type is clear and easy to read.

Few people have discussed the problems of hospitals without referring to the writings and opinions of Dr. Goldwater and everyone in the field of Hospital Administration consider him as their Dean. As one reads this book one is struck with the vast storehouse of authoritative knowledge concerning the multiplicity of subjects involved in the efficient operation of a hospital. It is noteworthy that of the five sections the greatest space is devoted to hospital planning, reflecting Dr. Goldwater's visions of the future, and that second place is given to hospital organization. The basic principles of hospital administration are contained in this section.

The section on Hospital, Patient and Community discusses the future of voluntary hospitals with particular emphasis on their methods of finance. Dr. Goldwater had been thinking of prepayment plans in connection with hospital finance since the turn of the century, and it is interesting to see how much of his early thinking has become the basis for the present plans and future thinking.

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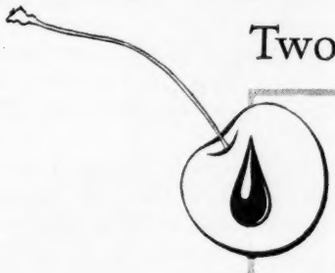

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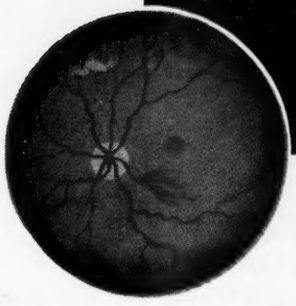

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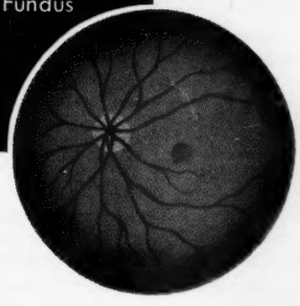

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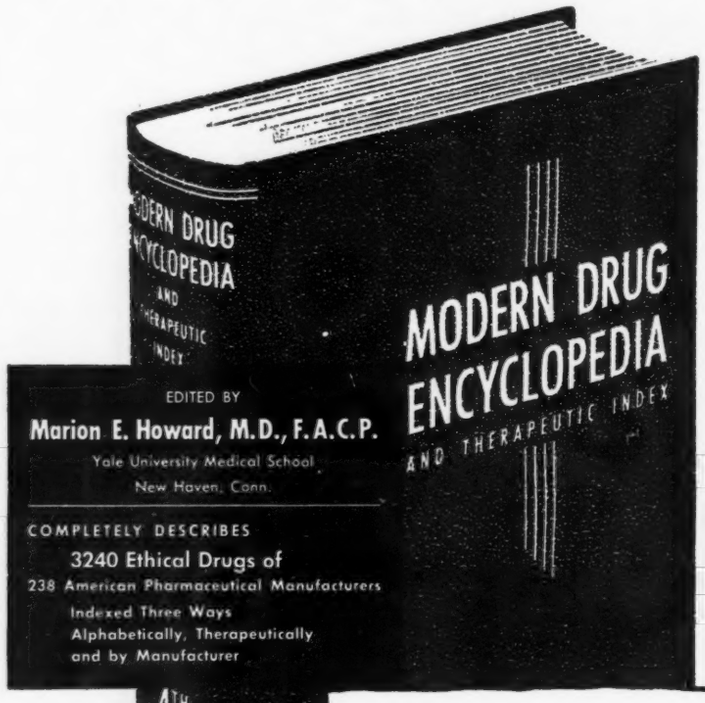

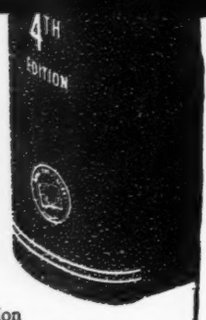

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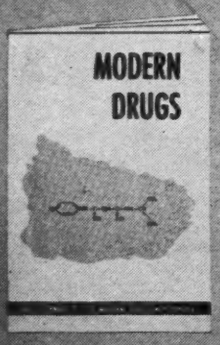

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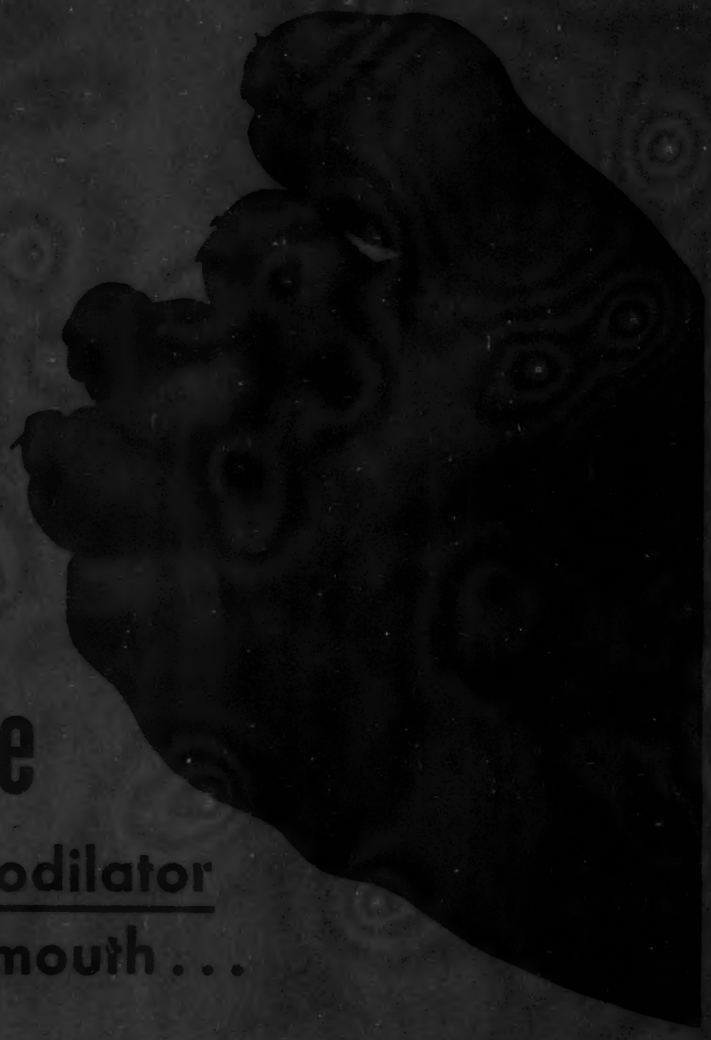

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